

# Exposure and Accumulation of Cadmium in Populations from Japan, the United States, and Sweden\*

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Studies were carried out in Japan, United States, and Sweden regarding comparability of analytical methods for cadmium, daily intake of cadmium via food, daily amount of cadmium in feces, concentrations of cadmium in different tissues and the body burden of cadmium, urinary excretion of cadmium and cadmium concentrations in blood. It was found that the cadmium intake via food among adults is about 35  $\mu\text{g/day}$  in Japan (Tokyo) and about 17  $\mu\text{g/day}$  in the U.S. (Dallas) and Sweden (Stockholm). It varies with age in a way similar to calorie intake.

Body burden increases rapidly with age. The half-time of cadmium is longer in muscles than in liver or kidneys. In the cross-sectional population samples studied (smokers and nonsmokers mixed) the average cadmium body burden at age 45 was about 21 mg in Japan, 9 mg in the U.S., and 6 mg in Sweden. Among nonsmokers in the U.S. and Sweden the body burden at age 45 was about 5-6 mg. The difference in average body burden for smokers and nonsmokers is explained by differences in smoking habits.

Cadmium excretion in urine was closely correlated with body burden and about 0.005-0.01% of body burden is excreted daily in urine.

Cadmium concentration in the blood was a good indicator of average recent intake over a 3-month period. Neither blood cadmium nor urine cadmium changed immediately after an increase of exposure level.

## Introduction

### Health Effects of Cadmium

Health effects of environmental cadmium have received considerable interest in recent years. Extensive reviews of toxicological aspects of cadmium have been published (1-7). The risks from occupational exposure to cadmium fumes or cadmium dust have long been well documented, and programs to monitor exposure and effects exist in most industrialized countries. Health effects of cadmium exposure in the general environment were acknowledged because of the occurrence of itai-itai disease and the high prevalence of proteinuria in cadmium-exposed

areas of Japan.

The acute and chronic health effects of cadmium exposure via air or food have been described in much detail. Acute exposure to high levels of cadmium in air may give a lethal pneumonitis, whereas chronic exposure to lower air levels may produce primarily emphysema and proteinuria. Acute exposure to cadmium via food causes vomiting, diarrhea and abdominal pain, whereas the major effects of chronic exposure in food is renal tubular dysfunction. The cadmium-induced proteinuria is a sign of such dysfunction.

It had been estimated that a long-term daily cadmium intake via food of 200-300  $\mu\text{g}$  may be associated with an increased prevalence of tubular proteinuria. The "normal" daily intakes were estimated to vary between 15 and 75  $\mu\text{g}$ , depending on country.

### The Need for Research

In 1972, when this cooperative study was planned, very few accurate data on the daily intake of cadmium were available. It was known that the U. S. industrial use of cadmium had doubled every

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decade since the beginning of this century, and that only a few percent of this Cd was recycled. The industrial use of zinc had increased in a similar way. This will also mean an increase in Cd exposure, as Zn and Cd are closely related both in nature and in industrial operations. Cadmium in air around point sources was known to contaminate soil and water, and cadmium in fertilizers and sewage sludge could be expected to increase the cadmium concentration in soil. Evidence has also accumulated concerning cadmium in cigarettes showing that cigarette smoking could be an important source of exposure.

In order to evaluate the risks of toxic effects in the general population, additional data on present daily cadmium intake was needed as well as data on absorption, distribution and excretion of cadmium. The autopsy data available showed that cadmium concentrations in renal cortex increased from almost none at birth to about 30–70  $\mu\text{g/g}$  at age 50. The age-related rate of increase indicated a very long (decades) half-time of cadmium in renal cortex.

The rapid increase of industrial use of cadmium and zinc pointed to the need to attempt retrospective measurement of daily intake and tissue levels. The limited data available in 1972 did not show any definite relationship between either blood or urinary cadmium and body burden or kidney concentration. Further data elucidating these relationships would be of value in order to select ways of monitoring individual intakes and kidney concentrations in the future.

Research into the health effects of cadmium was underway in Japan, the U.S., and Sweden. Some of these studies were conducted on a bilateral basis among the three countries. Furthermore, the exposure situation could be expected to vary between the countries, the exposure being highest in Japan and lowest in Sweden with the U.S. in between. These facts, taken together, indicated the desirability of a cooperative study involving all three countries simultaneously, using as far as possible comparable methods and taking advantage of the different situations in the three countries.

In this general introduction and in the introduction to each section reference will be made mainly to publications before this study was planned in order to indicate the level of knowledge at the time of the study. Later publications will be referred to in the discussion sections.

Studies carried out as a part of this cooperative project in each of the three countries are referred to by using the name of the country. It is well recognized, however, that all studies were limited to a particular geographic area within each country. There may be regional differences in cadmium concentrations in foodstuffs, tissues, etc., and the areas

chosen may or may not be representative of the whole country.

## Design of the Cooperative Study

The planning of the cooperative study occurred at a meeting in Tokyo in 1972. A protocol was set up which included six main areas for study (Fig. 1).

The present cadmium exposure via food was to be measured by cross-sectional studies on personal exposure estimated by fecal cadmium concentration. Inhalation exposure via cigarette smoking was to be estimated indirectly from data on body burden of cadmium. Environmental exposure would also be evaluated retrospectively by analyzing old food and cigarette specimens.

Body burden was to be estimated based on measurement of cadmium concentrations in kidney cortex, liver, pancreas and muscle from autopsy specimens of cases of sudden and accidental death. Duplicate sets of autopsy specimens were to be stored in tissue banks in order to facilitate future studies of time-related changes in body burden.

Excretion of cadmium from whole body and from renal cortex should be evaluated from cross-sectional studies on urinary cadmium excretion and comparison with body burdens and kidney concentrations.

The relationships between daily intake and blood and urinary cadmium were to be studied by analyzing consecutive specimens from persons with sudden increases in daily intake, e.g., newly employed workers.

All through these studies, comparisons of analytical results in the different laboratories were to be carried out. The atomic absorption techniques

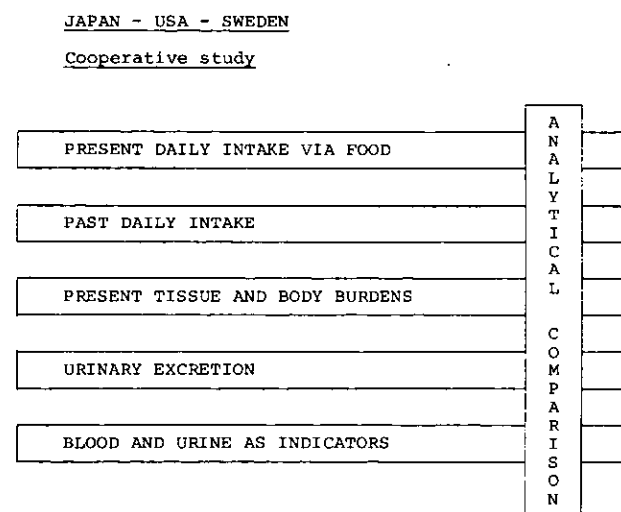


FIGURE 1. The six main items in the cooperative study.

Table 1. Outline of studies performed.

| Study                  | Types of specimens              | Participating laboratories <sup>a</sup> |
|------------------------|---------------------------------|---|
| Method studies         |                                 |   |
| I                      | Wheat, rice, urine              | Keio, IPH, EPA/SL, KI                   |
| II                     | Kidney, liver                   | Keio, EPA/SWRI, KI                      |
| III                    | Rice, wheat                     | Keio, IPH, EPA/SWRI, KI                 |
|                        | Feces                           | Keio, Gifu, EPA/SWRI, KI                |
|                        | Liver, urine                    | Keio, EPA/SWRI, KI                      |
|                        | Blood                           | SE, Keio, EPA/SWRI, KI                  |
| IV                     | Muscle, urine                   | EPA/SWRI, KI                            |
| Population studies     |                                 |   |
| Present exposure       | Feces                           | Keio, Gifu, EPA/SWRI, KI                |
| Past exposure          | Wheat, corn, beans              | IPH, EPA/SL, KI                         |
| Body burden            | Liver, kidney, pancreas, muscle | Keio, EPA/SWRI, KI                      |
| Excretion              | Urine                           | Keio, EPA/SWRI, KI                      |
| Indicators of exposure | Blood, urine                    | SE, EPA/SWRI, KI                        |

<sup>a</sup> Keio = Keio University, Japan; IPH = Institute of Public Health, Japan; Gifu = Gifu University, Japan; SE = Sanyo Electric Co., Japan; EPA = Environmental Protection Agency, U. S.; SL = Stewart Laboratories, U. S.; SWRI = Southwest Research Institute, U. S.; KI = Karolinska Institute, Sweden.

used in each laboratory would be compared with each other and with an independent technique such as neutron activation analysis. Such method studies should be performed on the different biological specimens to be analyzed. Throughout the study period, annual meetings between representatives of the three research groups have been held, at which time the program has been discussed. Based on accumulated experience, the protocol has been amended, partly to improve the program and partly because of infeasibility of certain studies. From the beginning it was expected that there would be problems encountered in performing certain studies. As will be seen below, however, most of the original plans were followed. An outline of studies performed and laboratories participating is seen in Table 1. A consensus on the content of this report was reached at a meeting in Florida, October 1976, with participants from all project groups. The final draft was circulated to all members of the cooperative study.

## Problems of Analysis

Since the purpose of this cooperative study was to estimate the cadmium exposure of nonoccupa-

tionally exposed populations in the three participating countries, it was imperative to assess the comparability of analytical methods used by participating laboratories in these countries. This assessment of comparability was complicated by both the variety of materials to be analyzed, e.g., food (especially grains), feces, tissues (e.g., kidney, liver), urine, and blood, and range of expected values from <1 ng/g to >100 µg/g. Although at the time of the agreement all participating laboratories were using methods based on atomic absorption spectrophotometry (AA), details of sample preparation and extraction procedures did vary between the laboratories. In Table 2 the major procedures and their abbreviations are listed. For most materials it was anticipated that AA would have a high accuracy, but it was known that materials with very low cadmium concentrations like urine and blood were difficult to analyze. A comparison of results of analysis of cadmium in urine between six laboratories in Japan (8) had shown a variation of ± 100% from the overall means. Normal urinary cadmium excretion was about 1 µg/24 hr in some studies (9, 10), but up to 40-100 µg/24 hr in other studies (11, 12). Interferences in cadmium analysis caused by sodium chloride and other salts (13) may explain the very high values in some studies.

## Methods of Interlaboratory Cross-Check of Analysis

The comparability of cadmium determinations by the participating labs was assessed by sending aliquots of samples of grains (wheat and rice), liver, blood, muscle, feces, and urine to each laboratory for analysis. Spiked water samples were also provided to the participating labs to investigate the accuracy of the final step of analysis. This comparison of cadmium analysis was carried out during the course of the rest of the cooperative studies. When the reasons for differences in analytical results could be identified, the methods were changed accordingly. In some cases it was then too late to repeat the initial study. The occurrence of problems of this kind as well as the details of preparations of samples and number of samples analyzed will be presented in the appropriate section below.

The samples for method study I and III (Table 1) were prepared and distributed by KI in Sweden. Keio prepared and distributed samples for method study II and EPA/SWRI carried this out for method study IV. The grain samples were dried. The liver, muscle, and feces samples were lyophilized and the blood, urine, and water samples stored in a refrigerator during preparation. All containers used for preparation or storage of samples had been acid

Table 2. Procedures used for analysis of the different materials.

| Material and Method <sup>a</sup>             | Laboratory                                       |                                     |                                     |                       |             |   |                                    |
|--|--|-------------------------------------|-------------------------------------|-----------------------|-------------|---|------------------------------------|
|  | Japan  |                                     |                                     | U.S.                  |             | Sweden  |                                    |
|  | Keio   | IPH                                 | Gifu                                | SE                    | SL          | SWRI  | KI                                 |
| Water solutions                              |  |                                     |                                     |                       |             |   |                                    |
| I <sup>b</sup>                               | F-AA/D <sub>2</sub>                              | F-AA                                | CR-AAS                              | HGA-AA/D <sub>2</sub> | —           | F-AA/D <sub>2</sub>   | HGA-AA/D <sub>2</sub> <sup>c</sup> |
| A <sup>c</sup>                               | None   | None                                | —                                   | LT/dry                | —           | None  | None                               |
| E <sup>d</sup>                               | None   | DDTC/MIBK                           | DDTC/MIBK                           | None                  | —           | DDTC/MIBK   | None                               |
| Feces  |  |                                     |                                     |                       |             |   |                                    |
| I  | F-AA   | —                                   | F-AA                                | —                     | —           | HGA-AA/D <sub>2</sub>   | F-AA/D <sub>2</sub>                |
| A  | HT-dry   | —                                   | HNO <sub>3</sub> /HClO <sub>4</sub> | —                     | —           | H <sub>2</sub> SO <sub>4</sub> /H <sub>2</sub> O <sub>2</sub> | HT-dry                             |
| E  | DDTC/MIBK  | —                                   | APDC/MIBK                           | —                     | —           | Amberlite/<br>Decane  | None                               |
| Grains                                       |  |                                     |                                     |                       |             |   |                                    |
| I  | —  | F-AA                                | —                                   | —                     | ES          | F-AA/D <sub>2</sub>   | HGA-AA/D <sub>2</sub>              |
| A  | —  | HNO <sub>3</sub> /HClO <sub>4</sub> | —                                   | —                     | dry and wet | HNO <sub>3</sub> -leaching                                    | HT-dry                             |
| E  | —  | None                                | —                                   | —                     | None        | DDTC/MIBK   | None                               |
| Tissues (liver, kidney,<br>pancreas, muscle) |  |                                     |                                     |                       |             |   |                                    |
| I  | F-AA/D <sub>2</sub>                              | —                                   | —                                   | —                     | —           | F-AA/D <sub>2</sub> <sup>e</sup>                              | F-AA/D <sub>2</sub> <sup>e</sup>   |
| A  | 3 acid   | —                                   | —                                   | —                     | —           | LT-dry  | HT-dry                             |
| E  | DDTC/MIBK  | —                                   | —                                   | —                     | —           | None  | None                               |
| Urine  |  |                                     |                                     |                       |             |   |                                    |
| I  | F-AA   | —                                   | —                                   | —                     | —           | HGA-AA/D <sub>2</sub>   | HGA-AA/D <sub>2</sub>              |
| A  | HNO <sub>3</sub> /H <sub>2</sub> SO <sub>4</sub> | —                                   | —                                   | —                     | —           | None  | HT-dry+HNO <sub>3</sub>            |
| E  | Dith/Chlor                                       | —                                   | —                                   | —                     | —           | APDC/MIBK   | APDC/MIBK                          |
| Blood  |  |                                     |                                     |                       |             |   |                                    |
| I  | F-AA/D <sub>2</sub>                              | —                                   | —                                   | F-AA/D <sub>2</sub>   | —           | HGA-AA/D <sub>2</sub>   | HGA-AA/D <sub>2</sub>              |
| A  | HNO <sub>3</sub> /H <sub>2</sub> SO <sub>4</sub> | —                                   | —                                   | 3 acid                | —           | None  | HT-dry+HNO <sub>3</sub>            |
| E  | DDTC/MIBK  | —                                   | —                                   | APDC/MIBK             | —           | DDTC/MIBK   | APDC/MIBK                          |

<sup>a</sup> Methods: I, instrumentation; A, ashing procedure; E, extraction procedure.

<sup>b</sup> Instrumental methods: AA, atomic absorption spectrophotometry; F-AA, regular flame AA; /D<sub>2</sub>, deuterium background correction; CR-AA, "carbon rod" flameless AA; HGA-AA, "heated graphite atomizer" flameless AA; ES, emission spectroscopy.

<sup>c</sup> Ashing procedures: LT, low temperature (< 200°C); HT, high temperature (> 400°C); dry, dry ashing; wet, wet ashing with acids. If acids are named, this would be the wet ashing procedure.

<sup>d</sup> Solvents: DDTC, diethyl dithiocarbamate; MIBK, methyl isobutyl ketone; APDC, ammonium pyrrolidine dithiocarbamate; Dith, dithizone; Chlor, chloroform.

<sup>e</sup> For samples with solution concentrations <0.1 µg/g, HGA-AA/D<sub>2</sub> was used instead.

washed or checked for cadmium contamination before use. Samples of sufficient size were prepared for the preparation of aliquots for all the laboratories participating in the study. The samples were homogenized by shaking and mixing before aliquots were taken. Each aliquot was given a unique code number and the people carrying out the analysis did not know the codes of the different samples, which should ensure blind analysis.

Other laboratories than KI, Keio, and EPA/SWRI were included in the method studies in order to further check the validity of analysis. Most of these laboratories used AA, but one used destructive neutron activation analysis (NA), which was used as a "reference" method. For details about the methods used, the reader is referred to a separate report of the method studies (Kjellström and Linnman, to be published) and to Table 2. The "reference" method (NA) was carried out in a similar way for all types of materials. The specimen was

irradiated, and nonradioactive carrier cadmium was added. After chemical and electrolytic separation of cadmium from other constituents, radioactivity was measured (14). Recovery was estimated by weighing the separated cadmium and comparing the amount to the added amount of carrier. A good agreement between AA and other techniques would indicate that a reasonable degree of confidence could be placed in the results.

In this section of the report only the results of the studies dealing with the water samples will be discussed, since the other results will be discussed in connection with the epidemiological studies undertaken.

### Comparison of Results in Final Analytical Step

Forty standard water solutions with additions of cadmium were distributed from the Karolinska In-

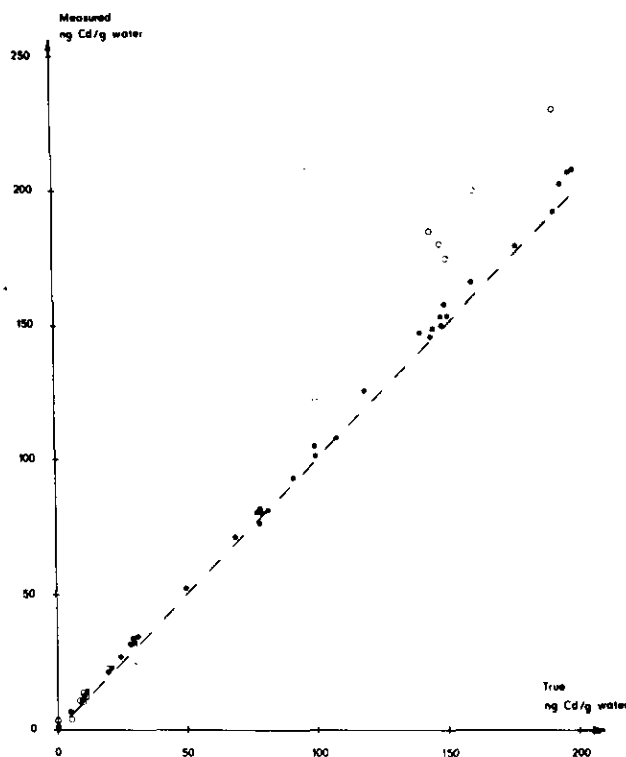


FIGURE 2. Comparison between the true standard concentrations and concentrations found in standard water solutions by the two laboratories with the smallest and greatest scatter in the 22-laboratory cross-check of analysis (Kjellström and Linnman, to be published).

stitute to 22 laboratories, not only in Japan, U.S., and Sweden, but also in other European countries than Sweden. Sodium chloride had been added to 10 of the solutions and phosphate to another 10. In most laboratories, AA after extraction in an organic solvent or flameless AA with background correction was used. Two laboratories used anodic stripping voltametry and another laboratory used NA.

The correlation coefficient between expected and observed values varied between 0.94 and 1.00. The results of these two "extreme" laboratories are depicted in Figure 2. Neither of these laboratories took part in any other cooperative study than the method study. When a large number of specimens is included even a correlation coefficient of 0.94 implies a considerable scatter. One would expect a better agreement between true and measured values than what is shown in Figure 2 for one of the laboratories, if a good method is used with skill for analysis of standard water solutions. The laboratory in Figure 2 with  $r = 1.00$  used F-AA after APDC/MIBK extraction for analysis, whereas the other laboratory used HGA-AA without other sample

preparation than dilution.

In the laboratories listed in Table 1 (participants in the cooperative study) and the NA laboratory, the correlation coefficients were above 0.96; the average recovery was between 90 and 103%. There was no laboratory where analysis of the solutions with addition of sodium chloride or phosphate gave systematic differences from the expected values. Thus, all methods used avoided the expected interferences. It was concluded that systematic differences between analytical results of the biological samples would not be caused by systematic errors in the final analytical step.

## Present Environmental Exposure

The major part of the general population's daily cadmium intake in Japan, the U.S., and Sweden comes via ingestion of food. Drinking water normally contributes very little. Also the contribution from ambient air is small, even around point sources (2). Cigarette smoking alone may cause a respiratory cadmium uptake similar to the uptake from food (15, 16).

When estimating the average daily cadmium intake via food, basically two different approaches can be used. One is to measure cadmium in food and the other is to measure cadmium in feces. The latter is feasible because only about 6% of ingested cadmium is absorbed (17). Animal experiments have shown that less than 0.05% of the body burden is excreted daily via the gastrointestinal tract (18, 19). Assuming that most of the daily cadmium intake comes via food, at steady state the excreted amount cannot exceed the 6% absorbed.

Cadmium analysis of individual foodstuffs and calculation of daily cadmium intake from data in dietary surveys, or cadmium analysis of homogenized total daily diet samples are the common ways of estimating daily intake by analysis of food. In the latter case, the diet samples could either consist of a set mixture of commonly used foods (market basket method) or of duplicates from actual diets consumed by persons in a study group (total diet collect method). Reported daily cadmium intakes using the food approach range from about 26  $\mu\text{g Cd/day}$  in the U.S. (20) to 60-113  $\mu\text{g Cd/day}$  in Japanese "low-exposure" areas (21). Estimates of daily cadmium intake via food can be obtained from data on cadmium in feces in two studies before 1972. The reported values were 31  $\mu\text{g Cd/day}$  in West Germany (22) and 30-47  $\mu\text{g Cd/day}$  in the U.S. (23). In this cooperative study the daily cadmium content of feces was used as the principal method for estimating cadmium intake via food. Some data on cadmium in whole diet samples will also be presented.

## Methods of Analysis

One comparative study of analysis of feces was carried out (Table 1). Aliquots of six homogenized lyophilized specimens were prepared and distributed from KI to the seven laboratories (2 g to each). The specimens were coded to ensure blind analysis.

At Keio, triplicate 2-g samples were wet-ashed in  $\text{HNO}_3/\text{H}_2\text{SO}_4$ . Cadmium was extracted with DDTC/MIBK and analyzed with regular flame AA using deuterium background correction.

At EPA/SWRI, duplicate 5-g samples were wet-ashed in  $\text{H}_2\text{SO}_4/\text{H}_2\text{O}_2$ . Cadmium was extracted with a combination of potassium iodide and Amberlite in decane. The final analysis was made with regular flame AA using deuterium background correction.

The KI method used duplicate 2-g samples (in the epidemiological study five 10-g samples from each specimen were used) which were dry-ashed at  $450^\circ\text{C}$  for 30 hr. Cadmium in the ash was dissolved with 1-M  $\text{HNO}_3$  and analyzed with flame AA with deuterium background correction.

Thus, the methods used were similar in many respects and so were the results of the analytical comparison (Fig. 3). The results of neutron activation (NA) analysis agreed well with the AA results. Only four of the 23 results in Figure 3 fell outside the ranges of  $\pm$  one standard deviation away from the sample means. The scatter of results from three other laboratories participating in the comparison tended to be greater than for the three laboratories mentioned above (Fig. 3), but the overall averages for all laboratories were close to the averages of the four laboratories (Fig. 3).

The average ratio between individual results from

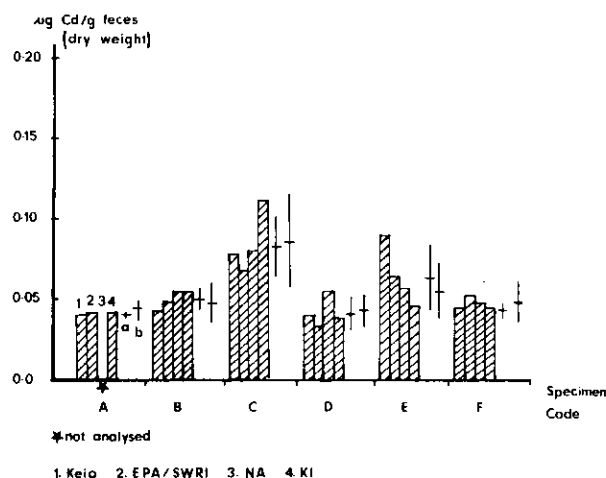


FIGURE 3. Results of the interlaboratory comparison of feces analysis: (a) average  $\pm$  standard deviation for the laboratories included in the figure; (b) average  $\pm$  standard deviations for all laboratories that analyzed feces in method study III.

Keio and the sample averages (for the four laboratories included in Fig. 3) was 1.02. The corresponding ratios were for EPA/SWRI 0.90, for NA 1.07, and KI 1.01. It was concluded that the agreement between the methods was acceptable. Analytical differences would not affect epidemiological comparisons more than a maximum of about 10%. In the epidemiological study Keio had changed from wet ashing to dry ashing ( $450^\circ\text{C}$  for 30 hr) of the feces specimens. An intralaboratory comparison of the two procedures on 10 specimens had given an average ratio between dry ashed and wet ashed aliquots of 0.97 and a correlation coefficient of 0.90 which was considered not to affect significantly the interlaboratory comparison of epidemiological results.

## Fecal Cadmium Content

In Japan, 24-hr feces specimens were collected for four consecutive days from 19 male and 17 female students in the age group 18–24 years, from 11 children under age 5, and from two 54-year old persons (24). All were living in Tokyo. The samples were weighed, mixed with a stick, and lyophilized before analysis. No data on smoking habits were collected.

In the U.S., feces specimens were collected at two occasions from 86 persons in the age range 2–59 (25). All were male volunteers in various occupations, living in Dallas, Texas. In order to estimate the average daily fecal amount an individual daily amount was calculated by taking half of the total amount for the two collects. This was considered acceptable because most Western people normally only defecate once a day. No fecal markers were used in this study. The samples were stored frozen. Before analysis the samples were thawed and thoroughly mixed with a glass stick. Information about smoking, medical, and work histories were collected in a standard questionnaire.

In the Swedish study 80 persons working at KI or their friends and relatives participated (26). The age range was 5–69 years, including 10 men in each 10 year age group and 10 women in the age group 20–29 years. During three consecutive days 24-hr specimens of feces were collected. The daily fecal amount for each participant was estimated as one third of the total 3-day amount. No fecal markers were used. After weighing and homogenization with a glass stick, subspecimens were taken for analysis from each 24-hr specimen. The smoking habits were recorded via a standard questionnaire.

In all three studies persons with occupational exposure to cadmium were excluded. The analysis of feces was carried out according to the methods de-

scribed in the previous section. The age group average cadmium concentration in feces was calculated based on individual feces specimens.

It was seen in the Swedish study (26) that the cadmium concentrations in fecal samples had a distribution closer to a log-normal than to a normal distribution, whereas the distribution of weights of feces samples were closer to a normal distribution. The evaluation of these agreements were made by comparing sums of square deviations between the distributions. These findings were confirmed in the American study (25). In the following treatise, geometric means (and standard deviations) will be used for cadmium concentrations in feces, and arithmetic means will be used for fecal amounts and daily fecal cadmium amounts.

The average fecal amounts in different age groups (Table 3) tended to be lowest in Japan and highest in the U.S. with Sweden in between. The differences were small. Except for the youngest age group there did not seem to be much variation with age. It was assumed that the calculated average fecal amounts would reflect the daily amounts of feces in each country. An earlier report from the U.S. (27) gave the daily average fecal amount for healthy adults as 115 g. This is slightly lower than most of the figures in Table 3, which, for instance, may be explained by changes in nutritional habits or differences between groups studied.

The ratios between cadmium concentrations in feces in Japan and the U.S. or Sweden were 2.5–3.5 (Table 3). There were no significant changes with age, but there was a tendency in the U.S. and Sweden for a slight decrease with age.

When the age-specific average daily fecal cadmium amounts are compared (Fig. 4), it is again

seen that the data from the U.S. and Sweden are similar. The variation with age in Sweden was shown to follow closely the variation of total daily energy intake with age (26). The results for Japanese men (Fig. 4) were about twice as high as the results from the other countries. In all the groups where comparisons between men and women could be made (Fig. 4), the daily fecal cadmium amount among women was about two thirds of the amount among men. This may reflect sex differences in energy intake.

A limited study of seven male medical students from Gifu, Japan (28), was carried out in connection with the cooperative study. Five consecutive 24-hr specimens were collected from each student. The average daily fecal cadmium varied between 41 and 79  $\mu\text{g}$  with an overall average of 56  $\mu\text{g}$ . The laboratory in Gifu participated in the interlaboratory crosscheck study of cadmium analysis (Kjellström and Linnman, to be published) and their results agreed well with the other laboratories. One additional study (EPA/SWRI) had been carried out in the U.S. (29, 30) on 216 volunteers from Houston in the age range 20–49. Overnight specimens of feces were collected, and 24-hr fecal amounts were not measured. The analytical method was different from the one used for the study in Dallas described above. The geometric average fecal cadmium concentrations in ten-year age groups varied between 0.17 and 0.23  $\mu\text{g/g}$  wet weight. These appear to be higher than those listed in Table 3. Some of the volunteers were parking attendants and may therefore have been occupationally exposed to cadmium in car exhaust fumes (29). Because of differences in analytical method and lack of data on total fecal amounts, daily fecal cadmium amounts were not

Table 3. Daily fecal amount and cadmium concentration in feces.

| Age   | Sex            | n  | Japan (Tokyo)                      |  | n  | U. S. A. (Dallas)                  |  | n  | Sweden (Stockholm) <sup>c</sup>    |  |
|-------|----------------|----|------------------------------------|--|----|------------------------------------|--|----|------------------------------------|--|
|       |                |    | Fecal amount                       | Cadmium in feces                         |    | Fecal amount                       | Cadmium in feces                         |    | Fecal amount                       | Cadmium in feces                         |
|       |                |    | mean $\pm$ S.D.,<br>g <sup>a</sup> | mean $\times$ S.D.,<br>$\mu\text{g/g}^b$ |    | mean $\pm$ S.D.,<br>g <sup>a</sup> | mean $\times$ S.D.,<br>$\mu\text{g/g}^b$ |    | mean $\pm$ S.D.,<br>g <sup>a</sup> | mean $\times$ S.D.,<br>$\mu\text{g/g}^b$ |
| 0–9   | M <sup>d</sup> | 7  | 66 15                              | 0.358 1.57                               | 15 | 91 47                              | 0.135 1.38                               | 10 | 89 34                              | 0.145 1.65                               |
|       | F              | 4  | 66 42                              | 0.177 2.14                               |    |                                    |  |    |                                    |  |
| 10–19 | M              | —  |                                    |  | 8  | 144 62                             | 0.127 1.58                               | 10 | 119 60                             | 0.142 1.83                               |
| 20–29 | M              | 19 | 117 61                             | 0.321 1.62                               | 16 | 131 63                             | 0.096 1.72                               | 10 | 130 50                             | 0.135 1.56                               |
|       | F              | 17 | 85 30                              | 0.298 1.43                               |    |                                    |  | 10 | 107 38                             | 0.131 1.84                               |
| 30–39 | M              | —  |                                    |  | 7  | 169 115                            | 0.093 1.62                               | 10 | 118 60                             | 0.143 1.72                               |
| 40–49 | M              | —  |                                    |  | 16 | 166 86                             | 0.116 1.49                               | 10 | 140 46                             | 0.126 1.66                               |
| 50–59 | M              | 1  | 135                                | 0.34                                     | 23 | 181 79                             | 0.104 1.47                               | 10 | 128 39                             | 0.138 1.47                               |
|       | F              | 1  | 113                                | 0.33                                     |    |                                    |  | —  |                                    |  |
| 60–69 | M              | —  |                                    |  | —  |                                    |  | 10 | 122 61                             | 0.110 1.77                               |

<sup>a</sup> Arithmetic means.

<sup>b</sup> Geometric means.

<sup>c</sup> Three specimens from each person.

<sup>d</sup> Average ages: Japan, 3 years; U.S., 5 years; Sweden, 5.5 years.

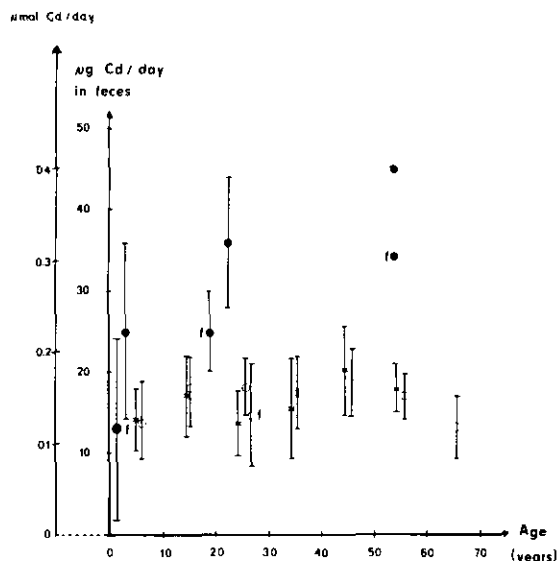


FIGURE 4. Daily amount of cadmium in feces (arithmetic mean and 95% confidence interval of mean) of groups in the three countries: (●) Japan; (X) U. S.; (○) Sweden; f denotes females.

calculated.

It was concluded that the average daily fecal cadmium at age 45 would be about 40  $\mu\text{g}$  in Japan, about 19  $\mu\text{g}$  in the U.S., and about 18  $\mu\text{g}$  in Sweden. These figures will be used for comparison with cadmium concentrations in different tissues.

The average daily fecal cadmium was slightly higher among smokers than among nonsmokers. In Sweden the 15 nonsmokers in the age range 20–59 had an average of 15.9  $\mu\text{g}$  Cd/day, whereas the 25 former and present smokers had 19.1  $\mu\text{g}$  Cd/day (25). In the U.S. the 49 nonsmokers in the age range 20–59 had an average fecal output of 16.7  $\mu\text{g}$  Cd/day and the 14 smokers had 19.5  $\mu\text{g}$  Cd/day (difference 2.8  $\mu\text{g}$  Cd/day).

In Sweden, 1.4  $\mu\text{g}$  of the difference between smokers and nonsmokers could be explained by a greater average fecal output among smokers than among nonsmokers and a difference of 1.8  $\mu\text{g}$  Cd/day in feces would be the result of smoking itself (26). This includes both the amount cleared from the respiratory tract that is swallowed and the amount that is excreted via bile and the intestinal cells. In the U.S. the smokers had a smaller average fecal amount than the nonsmokers (155 g as compared to 165 g) and the difference explained by smoking itself would therefore be 3.8  $\mu\text{g}$  Cd/day, slightly greater than the 2.8  $\mu\text{g}$  Cd/day given above.

## Cadmium in Food

In order to assess the agreement between daily intake estimates using the feces method and the

food analysis method, Keio collected total diet specimens for 20 consecutive days from Keio hospital in Tokyo (Iwao et al. to be published). Standard patient diets were prepared by hospital dietitians and all the food for each day was combined and homogenized. The average daily energy content in these specimens was 9.6 MJ and the average daily wet weight of food was 2400 g (= 530 g dry weight). Twenty specimens were analyzed with the same method as for feces. The average cadmium concentration was 0.07  $\mu\text{g/g}$  (dry weight, S.D. = 0.03), which corresponds to a daily total amount of cadmium in food of 35  $\mu\text{g}$ . This agrees well with the figures given above for cadmium amount in feces of adults from Tokyo.

No other studies on present cadmium intake via food were carried out as a part of the cooperative study, although during the course of the study some other analyses of foodstuffs took place in the participating laboratories. The average daily cadmium intake among adult men in Sweden was estimated at 17.2  $\mu\text{g}$  Cd/day (31) based on national average food consumption data and analysis of cadmium in wheat, vegetables, milk and meat products (the four main food items). This is very close to the average daily fecal amount of cadmium (18  $\mu\text{g}$ ) reported above.

## Cadmium in Tobacco

Samples of 18 different brands of cigarettes were analyzed by KI (32) with the same AA method that was used for grains and tissues (see other sections below). Brands sold in Sweden and Finland contained between 1 and 1.9  $\mu\text{g}$  Cd/cigarette, whereas those sold in Japan contained between 1.6 and 2.3  $\mu\text{g}$  Cd/cigarette. No cigarettes sold in the U.S. were analyzed.

The cadmium in mainstream smoke was collected on filters with a smoking machine that automatically smokes one cigarette at a time. The puff frequency can be varied. The puff size is 35 ml. Depending on puff frequency (1, 2, or 3 puffs/min) the cadmium amount in mainstream smoke of one brand of cigarette varied between 0.14 and 0.19  $\mu\text{g}$  Cd/cigarette (22 determinations). In this particular brand of cigarette the average total amount was 1.5  $\mu\text{g}$  Cd/cigarette. Thus, about 10% of the cadmium amount in the cigarette would be inhaled.

## Past Environmental Exposure

Because of the long half-time of cadmium in the critical organ, cross-sectional studies of cadmium concentrations in different tissues will show both age-related variations and cohort-related variations,



depending on changing average daily cadmium intake with time (33, 34). Studies of changes of daily cadmium intake with time would improve the accuracy of estimations of half-time based on age-related variations and could be of value for prognosis of future changes. With "past exposure" we mean the exposure decades previously.

The earliest extensive reports on cadmium in food came in the early 1960's (35, 36). The data referred to the U.S., and subsequent reports are available from the same country (27, 37). The estimates of daily cadmium intake via food vary between 4 and 71  $\mu\text{g/day}$  for the different studies, but there was no distinct trend with time. The target populations in early and late studies were not necessarily comparable, and differences in analytical methods may influence the validity of comparisons. It was the aim of the cooperative study to collect and analyze specimens of old foodstuffs like rice, wheat grains, tea leaves, and canned food in each of the three countries. In Japan and the U.S., only a few specimens were found, and the account below is based mainly on the Swedish results.

## Methods of Analysis

Two method studies of analysis of grain were carried out (method study I and III, Table 1). In

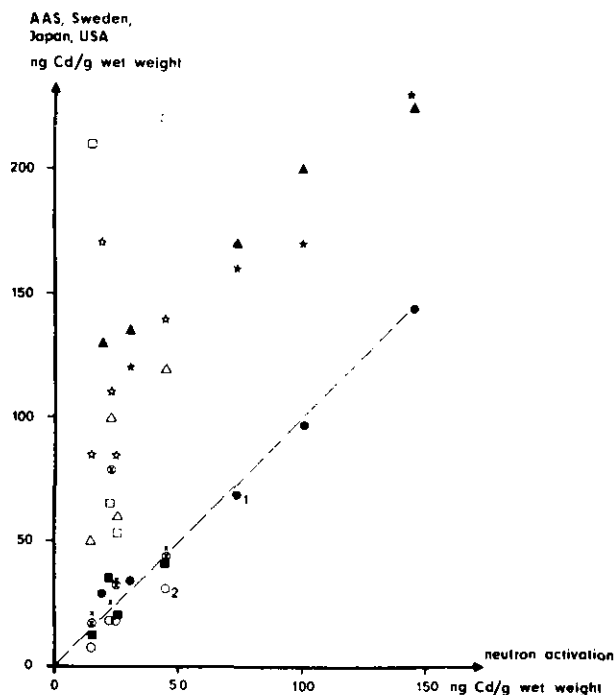


FIGURE 5. Comparison of cadmium analysis of wheat grains carried out in different laboratories, method study I (38). Each symbol denotes one laboratory.

method study I, cadmium analysis was compared on 10 wheat and 10 rice specimens distributed by KI to eight laboratories (38). The following methods were used by those participating in the past exposure study.

At IPH, 2-g samples of grain were dry-ashed at low temperature (125°C for 4 hr). The ashes were dissolved in  $\text{HNO}_3$  and cadmium analyzed with regular flame AA. Keio used a similar method; EPA/SL used optical emission spectroscopy after a combination of dry- and wet-ashing, and KI used HGA-AA/ $\text{D}_2$  after dry-ashing at 450°C for 30 hr of duplicate 4-g samples.

The analytical results of low-level ( $< 0.2 \mu\text{g/g}$ ) specimens of wheat and rice showed a good agreement between NA and AA at KI and two other laboratories not participating in the cooperative study (Fig. 5). Sparked source mass spectrometry was utilized in another laboratory (United States National Bureau of Standards), also with good agreement. However, AA analysis at Keio, IPH, and EPA/SL gave consistently 2–15 times higher values than the other laboratories.

The AA method used at the Karolinska Institute had been studied in detail by addition of radioactive cadmium (39). It had also been previously compared to NA on a large number of samples, whereupon the agreement was very good (40). Thus, there was reason to believe that the methods used at Keio, IPH, and EPA/SL gave erroneously high values.

One year later, another method-study was performed (method study III, Table 1) in which ten specimens of rice and five specimens of wheat were analyzed by eight laboratories (three outside the cooperative study). At Keio the analytical procedure had been changed so that  $\text{D}_2$  background correction was used with the flame AA and wet-ashing ( $\text{HNO}_3/\text{HClO}_4$ ) was now used at IPH instead of low-temperature dry-ashing. EPA/SWRI participated instead of EPA/SL in this second method-study. EPA/SWRI leached the cadmium from 3 g rice or wheat with 10 ml 1%  $\text{HNO}_3$  for 25 hr at room temperature. Cadmium was extracted from the leach solution by DDTC/MIBK and analyzed by F-AA/ $\text{D}_2$ .

The results are depicted in Figures 6 and 7. IPH still consistently had high values. On average the results of rice analysis at IPH were 3.7 times higher than the sample averages for all laboratories. The corresponding figure for wheat analysis was 1.47. This may be a result of the lack of extraction or  $\text{D}_2$  background correction at that laboratory. EPA/SWRI, on the other hand, had consistently low values. Results of analysis of rice and wheat were, on the average, 0.70 and 0.44 times the sample average

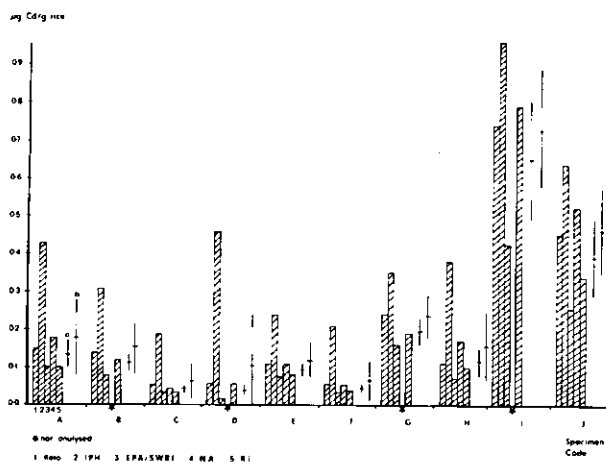


FIGURE 6. Comparison of cadmium analysis of rice grains carried out in different laboratories, method study III.

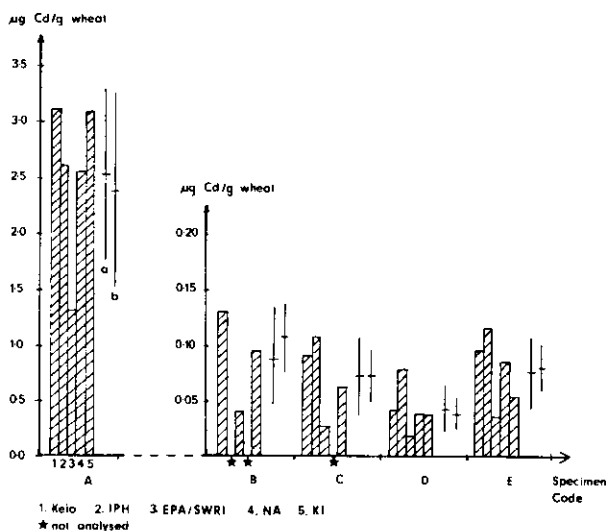


FIGURE 7. Comparison of cadmium analysis of wheat grains carried out in different laboratories, method study III. (a), (b) as in Figure 3.

for all laboratories. Losses caused by deficient ashing procedure may explain these results.

For the other three laboratories (Keio, NA, and KI) the agreement was satisfactory (Figs. 6 and 7). On the average, the results were 0.94 to 1.27 times the sample averages depending on material and laboratory.

## Old Food Specimens

After an enquiry in Sweden to museums and agricultural research laboratories and advertisements to the general public, 322 old specimens of grains (mainly wheat) were received, as well as old specimens of home-canned vegetables ( $n = 276$ ), mush-

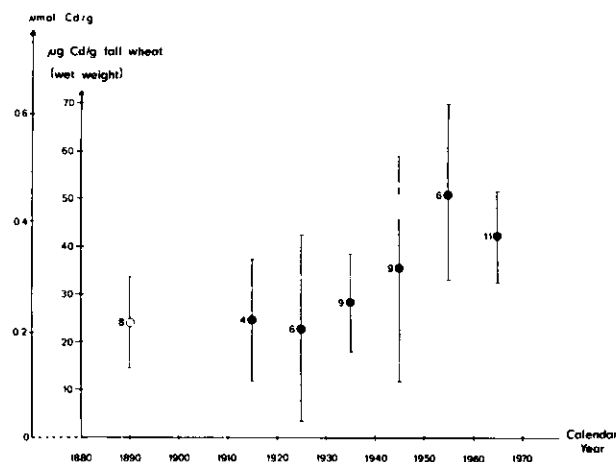


FIGURE 8. Average cadmium concentration in samples of fall wheat from Sweden harvested in different decades (41); 95% confidence intervals of mean indicated: (●) samples from the same fields in Uppsala; (○) samples from other parts of Sweden.

rooms ( $n = 152$ ), berries ( $n = 458$ ), fruit ( $n = 121$ ), meat ( $n = 210$ ), and fish ( $n = 61$ ). Many of the grain specimens were from the 19th century and other materials mostly contained specimens from 1915 onwards.

A series ( $n = 83$ ) of old Swedish specimens of fall wheat and spring wheat was analyzed (41). Most of the specimens had been harvested at the same farm fields and were of the same genotype through the years. There was a tendency for an increase of cadmium concentration with time. There was a considerable scatter in the data, and the increase was statistically significant only for fall wheat (Fig. 8). The average cadmium level in fall wheat doubled between the 1920's and the 1970's. Specimens of potato (1914–1974), carrots (1910–1974), and spinach (1917–1974) were also analyzed, but no significant changes in cadmium concentrations with time were seen (31).

Three old Japanese rice samples (1934–1951) were analyzed by IPH, and 15 old American grain samples (1921–1960) were analyzed by EPA/SL. The results were similar to results from recent specimens, but due to great variations in analytical results compared to the other laboratories, the time-related changes could not be evaluated.

## Old Tobacco Specimens

Fifteen specimens of cigarettes sold in Sweden between 1918 and 1970 were found in a tobacco museum. The cadmium concentrations were analyzed by KI by the AA method also used for grains and tissues. The results ranged between 1.0 and 6.5  $\mu\text{g Cd/cigarette}$  (32), and there was no ten-

dency for a systematic change in the cadmium amount with time.

## Present Body Burden

The body burden of cadmium in a "standard American man" (70 kg body weight) has been calculated as 30 mg (11). Friberg et al. (2) calculated from the limited available data that in Europe the corresponding figure would be 10–18 mg and in some Japanese "nonpolluted" areas, 40–80 mg. Because of the highly cumulative nature of cadmium, body burden estimates and estimates of population-average cadmium concentrations in the critical organ (kidney cortex) are of greater value for assessing the risk of cadmium-induced tubular damage in a particular population than the present daily intake levels. The relationship between present and past exposure levels, body burden, and blood or urine cadmium concentrations was not well known at the start of the cooperative study. Accurate and comparable data on cadmium body burden under different exposure situations in different countries were therefore in great need.

It had been estimated (2) that about a third of the body burden of cadmium is in the kidneys and a sixth is in the liver after long-term low level exposure. These organs were selected as major indicators of body burden, and in addition cadmium concentrations were measured in muscles, blood and pancreas.

For obvious reasons the specimens of internal organs had to be collected at autopsies. *In vivo* neutron activation analysis (42) is a new promising analysis method which may in the future enable us to carry out population studies of cadmium concentrations in different tissues of living people. Only persons who had died from sudden or accidental death were included in the cooperative study. This type of selection avoids inclusion of people with long-term illness that may have caused deterioration of kidneys and possible concomitant rapid changes in cadmium concentrations in the kidneys. On the other hand, there may be an overrepresentation of smokers in the group studied because they have higher mortality rates for accidents and sudden death than nonsmokers (43). Higher cadmium body burdens (15, 44) and higher urinary cadmium excretions (45) have been found among smokers than among nonsmokers. This agrees with the finding that cigarette smoking can contribute significantly to the daily absorbed amount of cadmium (see section "Present Environmental Exposure" above). Individual data on smoking habits are therefore important when measuring cadmium body burden.

## Methods of Analysis

Keio, EPA/SWRI, and KI participated in the epidemiological study of cadmium concentrations in liver, kidney, muscles and pancreas. Keio used 1-g specimens wet-ashed in  $\text{HNO}_3/\text{H}_2\text{SO}_4/\text{HClO}_4$ . Cadmium was extracted with DDTC/MIBK and analyzed with flame AA by use of  $\text{D}_2$  background correction. EPA/SWRI used duplicate 1-g specimens that were dry-ashed at low temperature ( $125^\circ\text{C}$  for 4 hr) in oxygen. The ashes were dissolved in  $\text{HNO}_3$  and cadmium was analyzed with flame AA and use of  $\text{D}_2$  background correction. KI used duplicate 2-g specimens that were dry-ashed at high temperature ( $450^\circ\text{C}$  for 30 hr). The ashes were dissolved in  $\text{HNO}_3$ , and analysis was carried out as for EPA/SWRI. For low-level specimens ( $<0.1 \mu\text{g Cd/g}$ ) HGA-AA was used instead of F-AA at EPA/SWRI and KI. NA was carried out as described above on 1-g specimens.

In a limited method study (No. II, Table 1) three specimens of each of frozen liver and kidney cortex were sent from Keio to KI and EPA/SWRI. There was a 10%–36% difference in average results (46). The differences may partly be explained by different degrees of drying of the specimens at analysis. Furthermore, the methods used in this method study were not exactly the same as those that were described above and were used in the epidemiological study. A more extensive method study was therefore carried out.

Aliquots of 10 lyophilized liver specimens were distributed by KI to the four laboratories mentioned

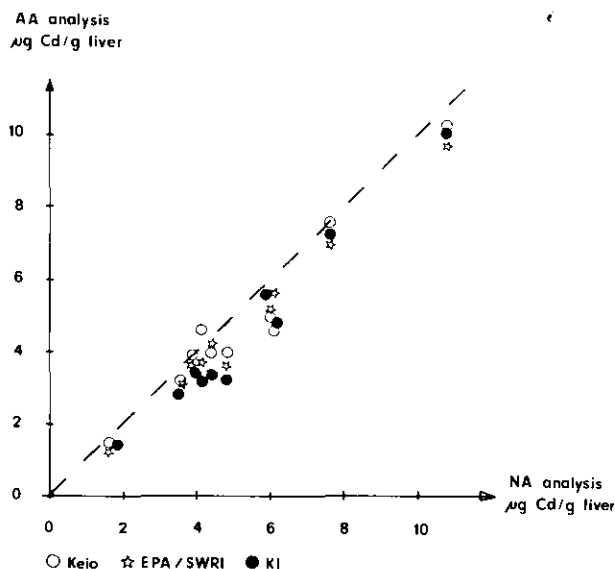


FIGURE 9. Results of atomic absorption analysis of cadmium in lyophilized liver specimens compared with results of neutron activation analysis.

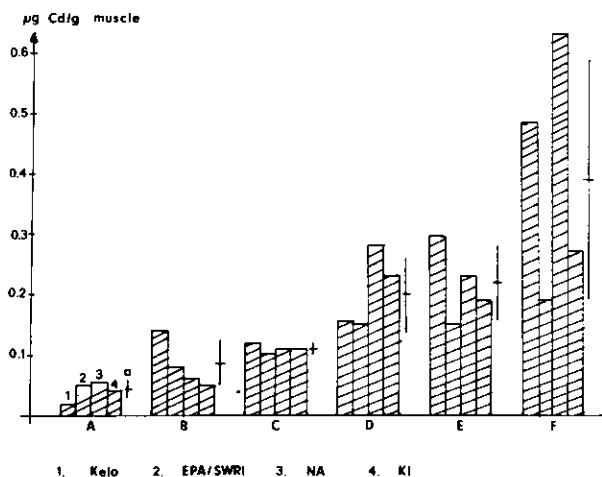


FIGURE 10. Comparison of cadmium analysis of muscle carried out in different laboratories, method study IV; (a) as for Figure 3.

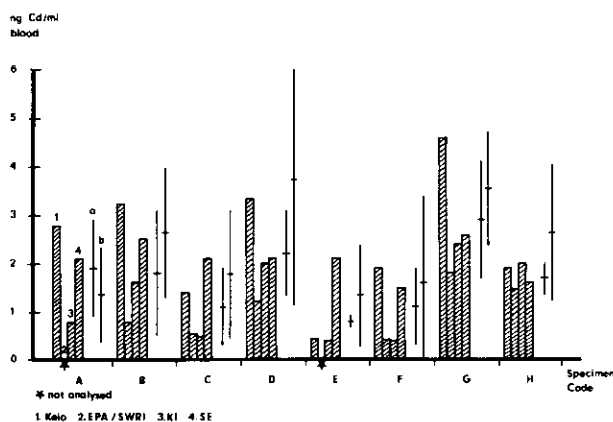


FIGURE 11. Comparison of cadmium analysis of blood carried out in different laboratories, method study III: (a), (b) as in Figure 3.

above and to an additional three laboratories (method study III, Table 1). There was a good agreement between all laboratories. The correlation coefficients (in the range 2–10 µg Cd/g lyophilized liver) between NA and Keio, EPA/SWRI and KI were +0.95, +0.97, and +0.98, respectively. As is seen in Figure 9 all these AA laboratories had slightly lower results than NA. On the average, the results from Keio were 1.02 times the sample averages for all laboratories. The corresponding figures for EPA/SWRI, NA, and KI were 0.98, 1.10, and 0.90. Aliquots of six lyophilized muscle specimens were distributed from EPA/SWRI to Keio, KI, and the NA laboratory (method study IV, Table 1). There was a greater variation in the muscle analysis results (Fig. 10) than in the results of liver analysis. The cadmium concentrations in muscle are about 10 times lower than the liver, and it is more difficult to

achieve a high and consistent accuracy at this level. Only in one sample (F) was there a considerable difference between AA results and NA results. The results from Keio were on the average 1.24 times the sample averages for all laboratories. For EPA/SWRI, NA, and KI the corresponding ratios were 0.84, 1.18, and 0.88. Thus, the differences in results between laboratories were not great.

A comparison of analysis of eight blood specimens distributed by KI to Keio, SE and EPA/SWRI was also carried out (method study III, Table 1). The samples had been heparinized and thoroughly shaken before separation of aliquots for each laboratory. During storage and transport the aliquots were kept frozen. An additional 10 other laboratories also analyzed these samples. NA analysis could not be carried out because of problems with its sensitivity in liquid samples. Keio used 5-g specimens, wet-ashed in HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>, extracted cadmium with DDTC/MIBK and analyzed with F-AA/D<sub>2</sub>. SE also used 5-g specimens, wet-ashed with three acids (HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>/HClO<sub>4</sub>), extracted with APDC/MIBK, and analyzed with F-AA/D<sub>2</sub>. EPA/SWRI extracted cadmium directly from 3 g blood with DDTC/MIBK and analyzed with HGA-AA/D<sub>2</sub>. KI used 2-g specimens that were both dry-ashed at high temperature and wet-ashed with HNO<sub>3</sub>. Cadmium was extracted with APDC/MIBK and analyzed with HGA-AA/D<sub>2</sub>.

Most of the results were in the range of 0.5–3 ng Cd/ml blood (Fig. 11). As a rule, the results of Keio and SE agreed well and were higher than those of EPA/SWRI and KI, which results were also well in accordance with each other. The results from Keio and SE were on the average 1.3 times the sample averages for all laboratories and the corresponding values for EPA/SWRI and KI were 0.55 and 0.67.

Ideally, these method studies should have been followed by modification of the methods and further interlaboratory comparisons of analysis until a very close agreement was found. Only after that should epidemiological studies begin by using verified analytical methods. Unfortunately this was not feasible in the present study, and intercountry comparisons must be made with the results of the method studies in mind.

It was concluded that for tissues with high cadmium levels (liver, kidney) there was a close agreement of analysis results (up to 10% systematic differences). Average analysis results of muscle differed up to about 40%, and results of blood analysis differed even more. For each type of tissue the average results from Japanese laboratories tended to be higher than results from other laboratories, and this has to be taken into consideration when the results of the epidemiological studies are evaluated.

## Cadmium in Liver and Kidney

In the epidemiological studies, samples from autopsies in Tokyo, Dallas, and Stockholm were analyzed. As mentioned above, liver and kidney cortex were collected at autopsies of cases of accidental or sudden death. The samples of liver (1–2 g) were taken from the left lobe and the samples of kidney cortex (1–2 g) were dissected as a 5 mm thick slice of the lower pole of one of the kidneys. The following account includes only those cases for which both liver and kidney cortex were analyzed. Further, only those data were included that were based on the analytical methods that had been crosschecked as discussed in the methods section above.

The numbers of people studied that fulfilled these criteria were 157 in Tokyo (men and women, age range 1–79), 164 in Dallas (men only, age range 10–59) and 285 in Stockholm (men and women, age range 2–89). The detailed data are given in Tables 4 and 5. It was shown in the Swedish study (47) that cadmium concentrations in both liver and kidney cortex follow log-normal distributions. The geometric averages and standard deviations are therefore

given in the tables along with the arithmetic averages and standard deviations, which would be more comparable with averages given in earlier publications. In each of the age- and sex-groups from each country, a log-normal distribution fitted the data better than a normal distribution.

As is seen in Tables 4 and 5, in most of the age groups where comparisons between data for males and females can be made, the averages for females were slightly higher. Because data only on males were collected in the U.S., the three-country comparisons will be based on the male data. In Japan no individual smoking habit data could be collected. No stratification for smoking habits were carried out in the initial comparisons between countries, but the possible influence of differences in smoking habits will be discussed below. The proportion of smokers in the Swedish group was the same for men and women, about 80%.

Figure 12 shows how the average cadmium concentration in liver increases with age in all three countries. There is a leveling off with increasing age, but it is difficult to estimate at what age this takes place. In kidney cortex (Fig. 13) there is a continuing increase up to age 40–60 and then a de-

Table 4. Cadmium concentrations in liver samples from autopsies.<sup>a</sup>

| Cd concentration, $\mu\text{g/g}$ wet weight |     |               |                              |                                 |                              |                              |                                 |                    |                 |                                 |
|--|-----|---------------|------------------------------|---------------------------------|------------------------------|------------------------------|---------------------------------|--------------------|-----------------|---------------------------------|
| Age  | Sex | Japan (Tokyo) |                              |                                 | U.S.A. (Dallas) <sup>b</sup> |                              |                                 | Sweden (Stockholm) |                 |                                 |
|  |     | <i>n</i>      | Mean $\pm$ S.D. <sup>c</sup> | Mean $\times$ S.D. <sup>d</sup> | <i>n</i>                     | Mean $\pm$ S.D. <sup>c</sup> | Mean $\times$ S.D. <sup>d</sup> | <i>n</i>           | Mean $\pm$ S.D. | Mean $\times$ S.D. <sup>d</sup> |
| 0-9  | M   | 15            | 0.60 0.80                    | 0.23 4.50                       | —                            | —                            | —                               | 5                  | 0.35 0.16       | 0.33 1.54                       |
|  | F   | 14            | 0.60 0.8                     | 0.27 3.61                       | —                            | —                            | —                               | 2                  | 0.16 —          | 0.15 —                          |
| 10-19  | M   | 5             | 2.0 0.7                      | 1.90 1.49                       | 34                           | 0.86 0.6                     | 0.68 2.12                       | 18                 | 0.66 0.45       | 0.55 1.82                       |
|  | F   | 5             | 2.5 2.2                      | 1.83 2.35                       | —                            | — —                          | — —                             | 6                  | 0.50 0.32       | 0.40 2.06                       |
| 20-29  | M   | 20            | 3.7 2.1                      | 3.27 1.70                       | 38                           | 1.1 0.6                      | 0.91 1.95                       | 18                 | 0.69 0.36       | 0.58 2.02                       |
|  | F   | 13            | 4.2 3.2                      | 3.23 2.14                       | —                            | — —                          | — —                             | 14                 | 0.73 0.39       | 0.63 1.76                       |
| 30-39  | M   | 18            | 3.1 2.1                      | 2.22 2.61                       | 33                           | 1.4 0.7                      | 1.20 1.80                       | 22                 | 0.86 1.09       | 0.51 2.80                       |
|  | F   | 7             | 4.0 1.6                      | 3.65 1.64                       | —                            | — —                          | — —                             | 12                 | 0.90 0.41       | 0.80 1.76                       |
| 40-49  | M   | 9             | 5.2 2.8                      | 4.52 1.82                       | 28                           | 1.4 0.8                      | 1.19 1.89                       | 24                 | 0.81 0.76       | 0.62 2.01                       |
|  | F   | 3             | 6.0 2.8                      | 5.58 1.55                       | —                            | — —                          | — —                             | 16                 | 0.99 0.66       | 0.79 2.07                       |
| 50-59  | M   | 9             | 3.7 2.6                      | 2.82 2.35                       | 31                           | 1.3 0.8                      | 1.05 2.11                       | 21                 | 1.07 0.83       | 0.77 2.56                       |
|  | F   | 4             | 5.2 3.2                      | 4.57 1.75                       | —                            | — —                          | — —                             | 22                 | 1.13 0.65       | 0.94 1.95                       |
| 60-69  | M   | 10            | 3.6 3.6                      | 2.67 2.15                       | —                            | —                            | —                               | 19                 | 1.11 0.81       | 0.84 2.26                       |
|  | F   | 4             | 5.5 3.5                      | 4.63 2.01                       | —                            | —                            | —                               | 20                 | 1.55 1.02       | 1.22 2.18                       |
| 70-79 (70+)                                  | M   | 8             | 4.6 3.1                      | 3.65 2.10                       | —                            | —                            | —                               | 20                 | 2.07 4.53       | 0.96 2.91                       |
|  | F   | 10            | 5.2 3.1                      | 4.01 2.28                       | —                            | —                            | —                               | 21                 | 2.21 4.25       | 1.14 2.69                       |
| 80-89  | M   | —             | —                            | —                               | —                            | —                            | —                               | 14                 | 0.89 1.25       | 0.59 2.21                       |
|  | F   | —             | —                            | —                               | —                            | —                            | —                               | 11                 | 0.79 0.83       | 0.46 3.67                       |

<sup>a</sup> Tables 4 and 5 include only the cases for whom both liver and kidney cortex were analyzed.

<sup>b</sup> These averages are not exactly the same as those reported by Johnson et al. (25). The table was based on preliminary data, some of which were later corrected by Johnson et al. Further, only cases for which both liver and kidney data were available were included here and Johnson et al. used a logit-transformation before calculation of average.

<sup>c</sup> Arithmetic mean and standard deviation.

<sup>d</sup> Geometric mean and standard deviation.

Table 5. Cadmium concentrations in kidney cortex samples from autopsies.

| Cd concentration, $\mu\text{g/g}$ wet weight |     |               |                              |      |                                  |      |                   |                              |      |                                  |      |                    |                              |      |                                 |      |
|--|-----|---------------|------------------------------|------|----------------------------------|------|-------------------|------------------------------|------|----------------------------------|------|--------------------|------------------------------|------|---------------------------------|------|
| Age  | Sex | Japan (Tokyo) |                              |      |                                  |      | U. S. A. (Dallas) |                              |      |                                  |      | Sweden (Stockholm) |                              |      |                                 |      |
|  |     | <i>n</i>      | Mean $\pm$ S.D. <sup>a</sup> |      | Mean $\times$ S. D. <sup>b</sup> |      | <i>n</i>          | Mean $\pm$ S.D. <sup>a</sup> |      | Mean $\times$ S. D. <sup>b</sup> |      | <i>n</i>           | Mean $\pm$ S.D. <sup>a</sup> |      | Mean $\times$ S.D. <sup>b</sup> |      |
| 0-9  | M   | 15            | 1.2                          | 1.1  | 0.79                             | 2.73 | —                 | —                            | —    | —                                | —    | 5                  | 3.30                         | 1.50 | 3.04                            | 1.58 |
|  | F   | 14            | 3.4                          | 5.5  | 1.1                              | 4.60 | —                 | —                            | —    | —                                | —    | 2                  | 1.34                         | —    | 1.32                            | —    |
| 10-19  | M   | 5             | 23.0                         | 8.6  | 21.0                             | 1.72 | 34                | 7.4                          | 3.9  | 6.5                              | 1.68 | 18                 | 8.57                         | 6.76 | 7.04                            | 1.81 |
|  | F   | 5             | 22.0                         | 16.9 | 15.7                             | 2.82 | —                 | —                            | —    | —                                | —    | 6                  | 6.45                         | 5.26 | 4.89                            | 2.25 |
| 20-29  | M   | 20            | 35.1                         | 18.5 | 29.9                             | 1.86 | 38                | 13.2                         | 6.1  | 11.7                             | 1.67 | 18                 | 13.0                         | 9.83 | 10.2                            | 2.07 |
|  | F   | 13            | 36.7                         | 19.9 | 32.2                             | 1.70 | —                 | —                            | —    | —                                | —    | 14                 | 12.6                         | 6.38 | 11.2                            | 1.67 |
| 30-39  | M   | 18            | 57.2                         | 23.8 | 51.9                             | 1.61 | 33                | 21.0                         | 10.1 | 18.6                             | 1.70 | 22                 | 22.2                         | 18.9 | 17.4                            | 1.98 |
|  | F   | 7             | 60.7                         | 19.8 | 58.5                             | 1.32 | —                 | —                            | —    | —                                | —    | 12                 | 21.6                         | 11.7 | 19.0                            | 1.70 |
| 40-49  | M   | 9             | 48.3                         | 24.7 | 43.2                             | 1.65 | 28                | 26.3                         | 11.9 | 23.1                             | 1.81 | 24                 | 22.3                         | 11.8 | 19.3                            | 1.80 |
|  | F   | 3             | 82.6                         | 35.9 | 82.7                             | 1.51 | —                 | —                            | —    | —                                | —    | 16                 | 29.0                         | 14.1 | 25.8                            | 1.65 |
| 50-59  | M   | 9             | 82.0                         | 56.9 | 65.0                             | 2.17 | 31                | 23.6                         | 13.9 | 21.0                             | 1.61 | 21                 | 20.5                         | 12.2 | 15.6                            | 2.48 |
|  | F   | 4             | 66.3                         | 24.5 | 63.2                             | 1.42 | —                 | —                            | —    | —                                | —    | 22                 | 26.6                         | 17.7 | 21.2                            | 2.05 |
| 60-69  | M   | 10            | 38.9                         | 24.1 | 32.9                             | 1.86 | —                 | —                            | —    | —                                | —    | 19                 | 19.2                         | 10.3 | 17.2                            | 1.61 |
|  | F   | 4             | 58.7                         | 31.0 | 49.2                             | 2.19 | —                 | —                            | —    | —                                | —    | 20                 | 24.4                         | 15.1 | 19.1                            | 2.22 |
| 70-79 (70+)                                  | M   | 8             | 48.7                         | 20.7 | 44.8                             | 1.56 | —                 | —                            | —    | —                                | —    | 20                 | 19.9                         | 31.9 | 12.6                            | 2.31 |
|  | F   | 10            | 64.8                         | 26.3 | 60.7                             | 1.44 | —                 | —                            | —    | —                                | —    | 21                 | 14.3                         | 10.8 | 11.6                            | 1.93 |
| 80-89  | M   | —             | —                            | —    | —                                | —    | —                 | —                            | —    | —                                | —    | 14                 | 10.2                         | 6.88 | 8.33                            | 1.95 |
|  | F   | —             | —                            | —    | —                                | —    | —                 | —                            | —    | —                                | —    | 11                 | 8.29                         | 7.93 | 6.36                            | 2.01 |

<sup>a</sup> Arithmetic mean and standard deviation.<sup>b</sup> Geometric mean and standard deviation.

creasing concentration with age. The age-related changes agreed with earlier reports from the three countries (35, 48, 49). Our data showed only small differences between Sweden and the U.S., whereas the Japanese results were generally about 4-5 times higher (Figs. 12 and 13).

Based on Tables 4 and 5 the ratios between cadmium concentrations in kidney cortex and liver were calculated (Table 6). In Japan and Sweden the ratios increase with age up to about age 40 and then decrease, reflecting the age-related changes in kidney cortex and liver cadmium concentrations. In the U.S. the ratios increase continuously with age from age 10 to 59. In each age group the ratios in Sweden are higher than the ratios in Japan. The U.S. ratios tend to be in between. It is known from animal experiments and autopsy data from industrial workers (2) that an increasing proportion of the body burden of cadmium will be in the liver at increasing exposure levels. The differences in kidney cortex to liver ratios between the three countries seen in this study may be related to the different exposure levels.

## Cadmium in Muscles

Samples of abdominal wall muscle were collected at autopsies from similar groups of people in the three countries. In the U.S. the study group was

identical to the group from which liver and kidney cortex specimens were collected (males, ages 10-59, *n* = 164) (Table 7). In Japan and Sweden the study groups for muscle analysis were only partly the same as the groups for liver analysis. Muscle specimens from 208 men and women in the age range 1-79 in Japan and 61 men and women in the age range 18-69 in Sweden were studied.

Both in Japan and Sweden the women had, in most age groups, higher average cadmium concentrations in muscle than men (Table 7). Among the men there was a continuous increase in cadmium concentration with age (Fig. 14) in each of the three countries. The results indicate that the half-time of cadmium in muscles is very long (several decades) and even longer than the half-time in kidney cortex (Fig. 13). The differences between the countries follow the same pattern as for liver and kidney cortex. In the U.S. the cadmium concentrations in muscle are about twice as high as in Sweden and in Japan they are about 5-10 times as high as in Sweden. Even though the method study for muscle did not give as good interlaboratory agreement as the method study for liver, only a small part of these differences could be explained by systematic differences in analytical results as described above.

There are no published extensive studies of cadmium in muscles with which these data can be compared.

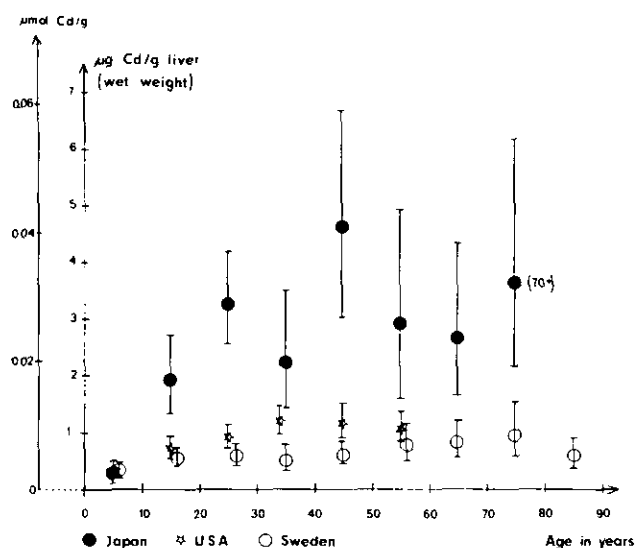


FIGURE 12. Average cadmium concentrations in liver of men in the three countries: (●) Japan; (X) U. S.; (○) Sweden; 95% confidence intervals of mean indicated.

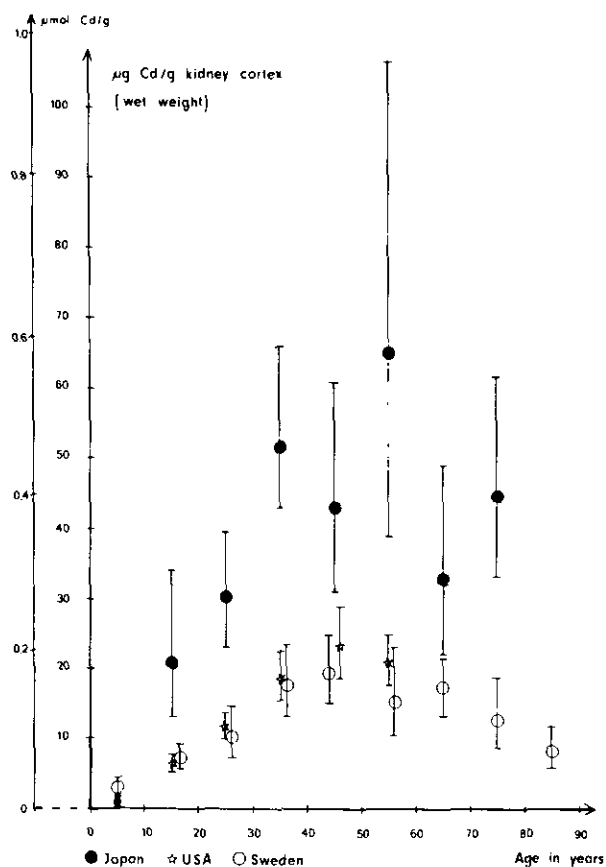


FIGURE 13. Average cadmium concentrations in male kidney cortex in the three countries: (●) Japan; (X) U. S.; (○) Sweden; 95% confidence intervals of mean indicated.

Table 6. Ratios between group average (geometric) cadmium concentrations in kidney cortex and liver.

| Age   | Sex | n  | Japan<br>(Tokyo)<br>ratio | n  | U.S.A.<br>(Dallas)<br>ratio | n  | Sweden<br>(Stockholm)<br>ratio |
|-------|-----|----|---------------------------|----|-----------------------------|----|--------------------------------|
| 0-9   | M   | 15 | 3.4                       | —  | —                           | 5  | 9.2                            |
|       | F   | 14 | 4.1                       | —  | —                           | 2  | 8.8                            |
| 10-19 | M   | 5  | 11.0                      | 34 | 9.6                         | 18 | 12.8                           |
|       | F   | 5  | 8.6                       | —  | —                           | 6  | 12.2                           |
| 20-29 | M   | 20 | 9.1                       | 38 | 12.9                        | 18 | 17.6                           |
|       | F   | 13 | 10.0                      | —  | —                           | 14 | 17.8                           |
| 30-39 | M   | 18 | 23.4                      | 33 | 15.5                        | 22 | 34.1                           |
|       | F   | 7  | 16.0                      | —  | —                           | 12 | 23.8                           |
| 40-49 | M   | 11 | 9.6                       | 28 | 19.4                        | 24 | 31.1                           |
|       | F   | 3  | 14.8                      | —  | —                           | 16 | 32.7                           |
| 50-59 | M   | 10 | 23.1                      | 31 | 20.0                        | 21 | 20.3                           |
|       | F   | 4  | 14.0                      | —  | —                           | 22 | 22.6                           |
| 60-69 | M   | 10 | 12.3                      | —  | —                           | 19 | 20.5                           |
|       | F   | 4  | 10.6                      | —  | —                           | 20 | 15.7                           |
| 70-79 | M   | 8  | 12.3                      | —  | —                           | 20 | 13.1                           |
|       | F   | 10 | 15.1                      | —  | —                           | 21 | 10.2                           |
| 80-89 | M   | —  | —                         | —  | —                           | 14 | 14.1                           |
|       | F   | —  | —                         | —  | —                           | 11 | 13.8                           |

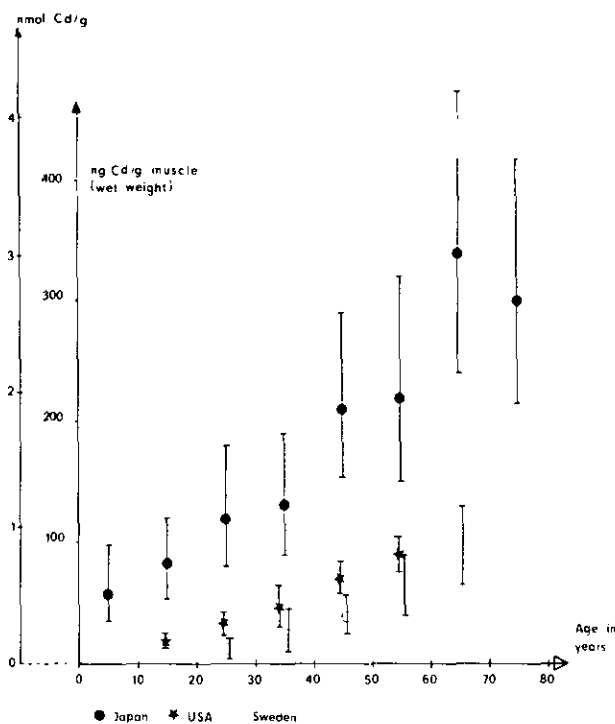


FIGURE 14. Average cadmium concentrations in male muscle in the three countries: (●) Japan; (X) U. S.; (○) Sweden; 95% confidence intervals of mean indicated.

Table 7. Cadmium concentrations in muscle samples from autopsies.

| Age   | Sex | Cd concentration, ng/g wet weight |                              |                                 |                 |                              |                                 |                    |                              |                                 |
|-------|-----|-----------------------------------|------------------------------|---------------------------------|-----------------|------------------------------|---------------------------------|--------------------|------------------------------|---------------------------------|
|       |     | Japan (Tokyo)                     |                              |                                 | U.S.A. (Dallas) |                              |                                 | Sweden (Stockholm) |                              |                                 |
|       |     | n                                 | Mean $\pm$ S.D. <sup>a</sup> | Mean $\times$ S.D. <sup>b</sup> | n               | Mean $\pm$ S.D. <sup>a</sup> | Mean $\times$ S.D. <sup>b</sup> | n                  | Mean $\pm$ S.D. <sup>a</sup> | Mean $\times$ S.D. <sup>b</sup> |
| 0-9   | M   | 21                                | 100 200                      | 60 2.98                         | —               | —                            | —                               | —                  | —                            | —                               |
|       | F   | 11                                | 50 30                        | 40 1.64                         | —               | —                            | —                               | —                  | —                            | —                               |
| 10-19 | M   | 6                                 | 100 100                      | 80 1.62                         | 34              | 30 20                        | 20 1.68                         | —                  | —                            | —                               |
|       | F   | 6                                 | 200 210                      | 140 2.61                        | —               | —                            | —                               | 1                  | 6                            | 6                               |
| 20-29 | M   | 14                                | 200 200                      | 120 2.19                        | 38              | 43 31                        | 34 1.95                         | 4                  | 12 6.5                       | 11 1.69                         |
|       | F   | 11                                | 140 120                      | 100 2.13                        | —               | —                            | —                               | 3                  | 14 5.1                       | 13 1.44                         |
| 30-39 | M   | 19                                | 200 200                      | 130 2.32                        | 33              | 50 27                        | 44 1.71                         | 7                  | 34 32                        | 24 2.58                         |
|       | F   | 7                                 | 270 210                      | 210 2.18                        | —               | —                            | —                               | 2                  | 38 8                         | 37 1.24                         |
| 40-49 | M   | 15                                | 200 200                      | 210 1.86                        | 28              | 77 34                        | 70 1.57                         | 13                 | 47 29                        | 38 2.03                         |
|       | F   | 9                                 | 430 400                      | 310 2.47                        | —               | —                            | —                               | 4                  | 74 40                        | 64 1.92                         |
| 50-59 | M   | 15                                | 300 200                      | 215 2.08                        | 31              | 95 34                        | 88 1.50                         | 9                  | 71 32                        | 62 1.81                         |
|       | F   | 9                                 | 570 240                      | 530 1.47                        | —               | —                            | —                               | 5                  | 89 74                        | 73 1.9                          |
| 60-69 | M   | 21                                | 500 600                      | 340 2.15                        | —               | —                            | —                               | 9                  | 107 56                       | 94 1.71                         |
|       | F   | 6                                 | 420 200                      | 390 1.51                        | —               | —                            | —                               | 4                  | 144 64                       | 134 1.55                        |
| 70+   | M   | 21                                | 400 400                      | 300 2.17                        | —               | —                            | —                               | —                  | —                            | —                               |
|       | F   | 18                                | 500 350                      | 370 2.47                        | —               | —                            | —                               | —                  | —                            | —                               |

<sup>a</sup> Arithmetic mean and standard deviation.<sup>b</sup> Geometric mean and standard deviation.

## Cadmium in Blood

In the cooperative study, cadmium concentrations in blood were studied mainly with the aim of elucidating how blood cadmium reflected daily intake or body burden. No systematic cross-sectional studies covering a large age range were therefore carried out. Some data were collected that can be used to calculate the contribution to cadmium body burden from blood.

In Japan (SE laboratory) vein blood cadmium was analyzed for 213 male newspaper factory workers in the age range 20-55 years. They had no occupational cadmium exposure (50). The overall arithmetic average was 4.5 ng Cd/g blood (S.D. = 2.6 ng/g). No data on smoking habits had been collected. It was reported (50) that the background correction in the analysis (F-AA/D<sub>2</sub> after extraction) amounted to about 50% of the total absorption in the AA analysis. This again points to the problems of analysis of cadmium in blood discussed above.

In the U.S., 216 males and females (age range 18-53 years) from Houston were studied by SWRI in connection with a survey of lead exposure from automobile exhausts (29). The group included policemen, garage attendants, and housewives. Individual data about smoking habits were collected. The analysis of cadmium in vein blood was carried out with the Delves cup AA technique instead of the one used for the interlaboratory cross-check of cadmium analysis (EPA/SWRI).

The overall arithmetic average cadmium concen-

tration in blood was 4.9 ng/g (S.D. = 1.5 ng/g) for the 127 men and 6.5 ng/g (S.D. = 2.4 ng/g) for the 89 women. There were no obvious variations with age of cadmium concentration in blood within this age range. The 77 smoking men had 5.2 ng Cd/g blood as compared with 4.5 ng Cd/g blood for the 50 nonsmoking men. The 49 smoking women had 6.0 ng Cd/g blood and the 40 nonsmoking women had 7.2 ng Cd/g blood. A systematic effect of smoking on blood cadmium could therefore not be seen in these data.

In Sweden 39 newly employed workers in a cadmium battery factory were studied. Venous blood samples were collected before cadmium exposure began. The overall arithmetic average was 4.5 ng Cd/g blood (S.D. = 2.1 ng/g) when the method described above was used (KI). All samples were also analyzed with a Delves cup AA method. The overall average result using this method was 3.1 ng Cd/g blood. There seemed to be a systematic difference of 1-2 ng/g between these two methods at KI. There was no tendency for a difference between the 27 men and the 12 women in the group, but the smokers had on average higher results than the nonsmokers. The average results were for the HGA-AA method 3.0 ng/g (nonsmokers) and 4.8 ng/g (smokers) and for the Delves cup AA method 1.4 ng/g (nonsmokers) and 3.4 ng/g (smokers).

Due to the uncertainties of the comparability of the different analytical techniques, no quantitative comparison between the three countries can be made. The Swedish data seem to be lower than the



other data, but the difference is about the same as the difference in analytical results seen in the inter-laboratory cross-check. The results are of the same magnitude as reliable data in earlier reports (9, 51). Some other earlier reports reviewed by Friberg et al. (2) gave cadmium concentrations in blood that were obviously erroneously high due to inaccurate analytical methods. Higher blood cadmium concentrations among smokers than among nonsmokers have also been reported (52). It was found that nonsmoking adults in Sweden had an average about 0.5 ng Cd/g blood and smokers had an average about 2 ng Cd/g (Delves cup AA).

For the calculation of the contribution of blood cadmium to cadmium body burden, it was decided to use a range instead of a single number. It was estimated that in each of the three countries the average adult cadmium concentration in blood would be between 1 and 6 ng Cd/g. A smoker would have about 1 ng Cd/g higher value than a nonsmoker.

### Cadmium in Other Tissues

Analysis of other tissues, like pancreas and fat, was carried out to a more limited degree than the analysis of liver and kidney cortex. The pancreas cadmium levels in Sweden were similar to liver cadmium levels (47), and the fat cadmium levels were similar to the muscle cadmium levels (Kjellström and Elinder, to be published). In the body burden estimate below, pancreas was included as a separate tissue even though its weight is very small. The analytical comparability between the three countries was assumed to be the same as for liver. Detailed data will not be given here, as they have been published elsewhere (25, 46, 47). In the group of men between 30–59 years (the group used for the body burden calculations below) the geometric average cadmium concentrations (wet weight) in pancreas were 2.2  $\mu\text{g/g}$  (Japan), 0.70  $\mu\text{g/g}$  (U. S.), and 0.50  $\mu\text{g/g}$  (Sweden).

In order to estimate the contribution to cadmium body burden from tissues other than liver, kidney cortex, muscle, blood, and pancreas, it was assumed that the ratio between cadmium concentration in these other tissues and the concentration in muscles was the same as in the report by Sumino et al. (53). They analyzed the cadmium concentration (flame AA after extraction in DDTC/isopropyl acetone) in 19 different tissues from 30 Japanese (age range 15–65 years) living in a nonpolluted areas. The estimated average weights for each tissue were given and by multiplying these weights with average cadmium concentrations, a weighted average cadmium concentration in "other tissue"

(15 tissues; excluding liver, kidney, pancreas, and muscle) could be calculated. The ratio between this weighted average cadmium concentration in "other tissues" (0.19  $\mu\text{g Cd/g}$ ) and average cadmium concentration in muscles was 0.64.

### Calculation of Body Burden

Our aim was to calculate the body burden of an average 45-year old man in the 1970's for each country. Cadmium concentrations in the different tissues in the age range 30–59 years were used for the calculations. In Figure 15 the distributions of data for the three countries were plotted. Cadmium concentrations in urine were also included for comparison. It is seen that between each of the four tissues included in the figure there is roughly one order of magnitude difference in cadmium concentrations. Most of the observed distributions fit very well to log-normal distributions.

The initial calculation of body burden is based on the whole group studied regardless of smoking habits. It was assumed that the cadmium concentrations in kidney cortex were 50% higher than in the whole kidney (54). The weights of the different tissues in the U.S. and Sweden are those given for "reference man" (55). Corresponding weights for an average Japanese person were given by Sumino et al. (53). The concentrations in kidneys, liver, pancreas, and muscles used in the calculation were based on the geometric average for 30–59 year old men as reported by each laboratory (Fig. 15). For a Japanese 45-year old man the cadmium body burden is the highest (about 21 mg). The American cadmium body burden is about 8.7 mg and the Swedish about 6.4 mg (Table 8). These estimates all refer to mixed smoker–nonsmoker populations as they occurred in the epidemiological studies. Only a fraction of the differences between the countries could be caused by analytical differences (see above).

### Past Body Burden

As was mentioned in the section on past exposure, the long half-times of cadmium in many body tissues make it important to study secular changes of exposure or body burden in order properly to evaluate findings in cross-sectional studies. The body burdens of cadmium in old people reflect both recent exposure and past exposure, but data about present body burdens only cannot be used to estimate how the exposure levels have changed with time.

The only feasible way to study past body burden would be to analyze tissue specimens from autop-

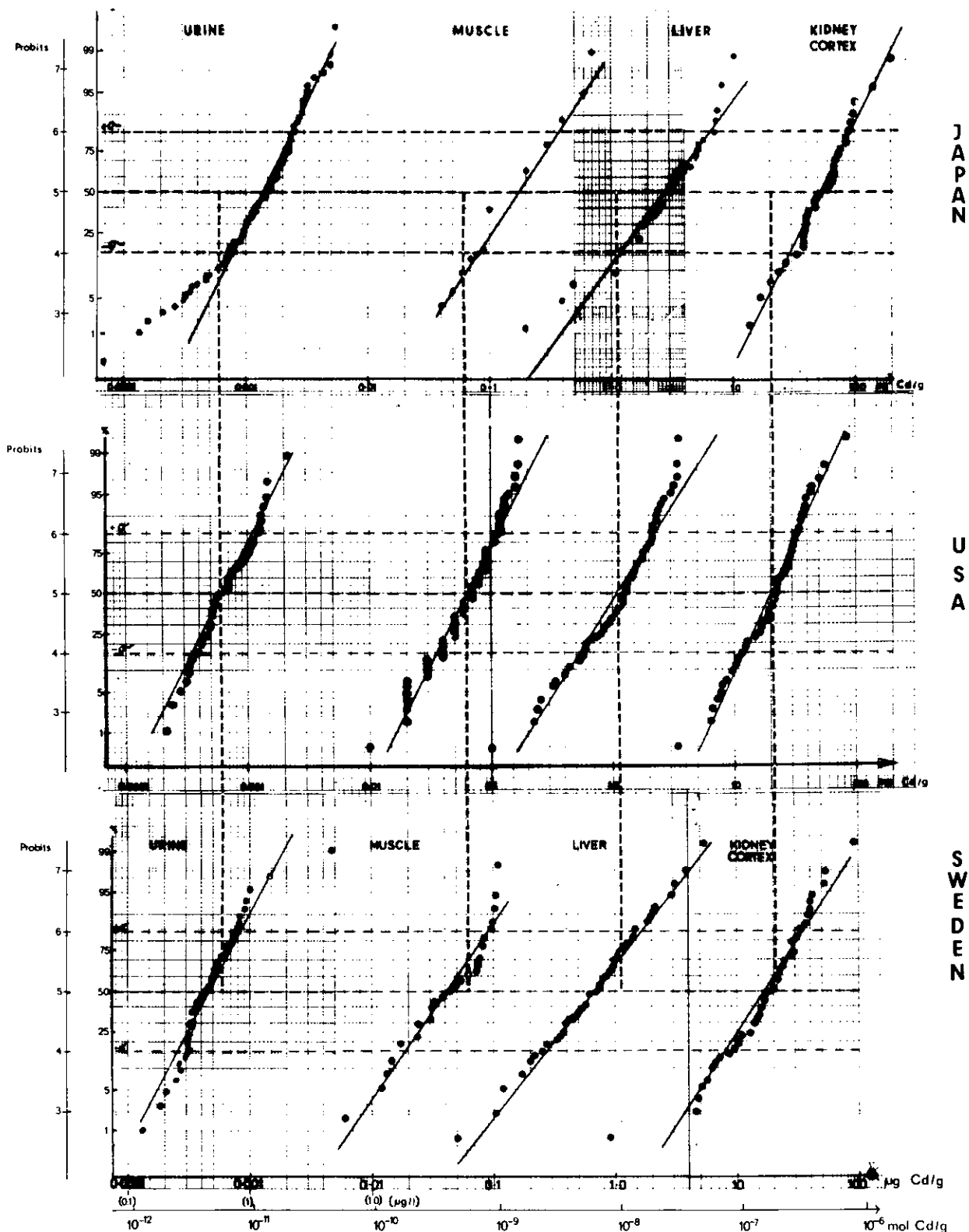


FIGURE 15. Cumulative distributions of cadmium concentrations in four tissues. Men, age range 30-59; smokers and nonsmokers combined. Vertical dotted lines through the median of the USA data included to facilitate comparison between the distributions.

**Table 8. Estimated organ and body burdens of a 45 year old "reference" man.**

| Type of organ             | Organ weight         | Organ and body burdens, mg <sup>a</sup> |                              |                                 |
|---------------------------|----------------------|---|------------------------------|---------------------------------|
|                           |                      | Japan (Tokyo) <sup>b</sup>              | U.S.A. (Dallas) <sup>c</sup> | Sweden (Stockholm) <sup>c</sup> |
| Kidneys <sup>d</sup>      | 260 g <sup>b</sup>   | 9.5                                     | 3.9                          | 3.3                             |
|                           | 300 g <sup>c</sup>   | (37)                                    | (13)                         | (11)                            |
| Liver                     | 1200 g <sup>b</sup>  | 3.4                                     | 1.7                          | 1.0                             |
|                           | 1500 g <sup>c</sup>  | (2.8)                                   | (1.1)                        | (0.68)                          |
| Pancreas                  | 60 g <sup>b</sup>    | 0.13                                    | 0.049                        | 0.035                           |
|                           | 70 g <sup>c</sup>    | (2.2)                                   | (0.70)                       | (0.50)                          |
| Muscles                   | 26 kg <sup>b</sup>   | 4.7                                     | 1.8                          | 1.2                             |
|                           | 30 kg <sup>c</sup>   | (0.18)                                  | (0.060)                      | (0.040)                         |
| Blood                     | 4.6 kg <sup>b</sup>  | 0.005-0.028                             | 0.006-0.032                  | 0.006-0.032                     |
|                           | 5.4 kg <sup>c</sup>  | (1-6 ng/g)                              | (1-6 ng/g)                   | (1-6 ng/g)                      |
| Rest of body <sup>e</sup> | 27.6 kg <sup>b</sup> | 3.3                                     | 1.2                          | 0.85                            |
|                           | 32.5 kg <sup>c</sup> | (0.12)                                  | (0.038)                      | (0.026)                         |
| Total body                | 60 kg <sup>b</sup>   | 21                                      | 8.7                          | 6.4                             |
|                           | 70 kg <sup>c</sup>   |   |                              |                                 |

<sup>a</sup> Concentrations ( $\mu\text{g/g}$ ) used for the calculations are given in parentheses. Smokers and nonsmokers are mixed. The calculation includes also those cases for whom smoking habits were unknown. Among the cases for whom smoking habits were known, present or former smokers constituted 77% in the American group and 82% in the Swedish group.

<sup>b</sup> Data of Sumino et al. (53).

<sup>c</sup> Data from "reference" man (55).

<sup>d</sup> It was assumed that concentration in kidney cortex was 50% higher than in whole kidney.

<sup>e</sup> Concentrations are 64% of concentration in muscles, based on assessment of data by Sumino et al. (53).

sies carried out long ago. The storage procedure must be suitable so that losses or contamination does not occur.

## Cadmium in Old Kidney Specimens

Old tissue specimens for analyses in the cooperative study were collected only in Sweden. Thirty-three specimens of adult human kidneys from autopsies during 1880-1899 were found in anatomical museums (56). The specimens had been stored in alcohol or formalin and were all in good anatomical condition. Small (1 g) samples of kidney cortex were taken from each kidney so as not to damage the specimens. Cadmium concentrations in these samples were analyzed at KI with the AA method for kidney described above.

The cadmium content of the storage liquids were also analyzed by the same method. The cadmium concentrations in these liquids were generally very much lower than the concentrations in the kidneys. A two-year experiment with two fresh kidneys stored in ethanol showed that losses of cadmium from tissue to storage liquid were small (56). By also taking the individual kidney weights and storage

liquid weights into account it was estimated that any possible losses of cadmium from the kidneys to the liquid must have been very small (56).

In order to avoid bias caused by different moisture content of fresh kidneys and old kidneys, dry weight based values were used for the comparison between new and old kidneys. The geometric mean cadmium concentration in kidney cortex of the 33 adults from the 19th century was  $15 \mu\text{g Cd/g}$  dry weight (96% confidence limits of mean was 11-20  $\mu\text{g/g}$ ). The corresponding figure for 39 nonsmoking adults who died in 1974 was  $57 \mu\text{g Cd/g}$  dry weight (95% confidence interval; 46-71  $\mu\text{g/g}$ ). These data support the data in the section on past exposure showing an increased concentration of cadmium in certain foodstuffs (Fig. 7) with time.

## Urinary Excretion after Long-Term Exposure

Both animal and human data (2) indicate that urine is one of the major excretion media for cadmium. Fecal excretion of cadmium has not been quantified in humans but in animals it is of the same magnitude as urinary excretion (19). Urinary excretion of cadmium has been used in a number of studies to estimate exposure in both occupationally exposed groups and groups exposed via food. The relationship between urinary excretion and body burden or exposure in human beings is not very well known, however. Furthermore, animal experiments have shown that cadmium excretion increases drastically when cadmium-induced renal tubular damage occurs (57).

The aim with the urinary cadmium excretion analyses in this cooperative study was to compare urinary excretion with present daily intake and present body burden in comparable general population groups. Clustered samples according to age group were selected from the three countries (Tokyo, Dallas, and Stockholm). The people in the autopsy studies had died from accidental or sudden death. There may therefore be a higher proportion of smokers in the autopsy groups (see section on Present Body Burden, above) than in the groups of the general population in which urinary excretion was studied. Otherwise there was no reason to believe that the groups selected for the body burden studies and the urinary excretion studies would have different average cadmium intakes.

## Methods of Analysis

In method study I (Table 1) samples of urine with a cadmium concentration range from less than 1  $\mu\text{g/l.}$  to 30  $\mu\text{g/l.}$  were analyzed in four laboratories

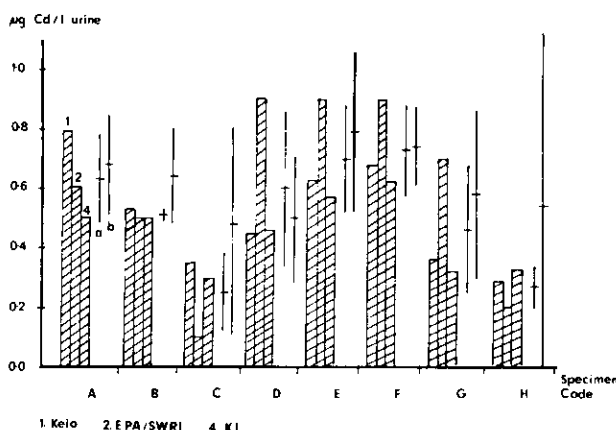


FIGURE 16. Comparison of cadmium analysis of urine carried out in different laboratories; method study III; (a), (b) as in Figure 3.

by using AA and in one laboratory by using NA (38). Generally these were relatively high cadmium concentrations in urine and there was a good correlation between AA laboratories and the NA laboratory in the whole group of specimens ( $r = 0.96-0.98$ ). However, in the two specimens with the lowest cadmium concentrations ( $< 1 \mu\text{g/l.}$ ), NA could not detect cadmium and there was a great difference among the AA laboratories (including Keio, IPH and KI). In "normal" urines the cadmium concentrations are usually below  $1 \mu\text{g/l.}$  (2), and it was therefore decided to carry out a further method study on the low level samples.

Eight frozen urine specimens were distributed from KI to 11 other laboratories as a part of method study III. All specimens were from "normal" Swedes and the expected cadmium concentrations were  $< 1 \mu\text{g/l.}$  NA could not detect cadmium in any of the specimens. Two of the AA laboratories gave results one order of magnitude higher than all the other AA laboratories and were excluded from the comparison in Figure 16. Keio used 100 ml samples that were wet-ashed in  $\text{HNO}_3/\text{H}_2\text{SO}_4$ . Cadmium was extracted with dithizone/chloroform and analyzed with regular F-AA. At SWRI, cadmium was extracted directly from 10 ml urine with APDC/MIBK and analyzed with HGA-AA/ $\text{D}_2$ . KI used 25 ml urine that was both dry-ashed at  $450^\circ\text{C}$  for 30 hr and wet-ashed in  $\text{HNO}_3$ . From an acid solution of the ashes cadmium was extracted with APDC/MIBK and analyzed with HGA-AA/ $\text{D}_2$ .

The individual results for these three laboratories are given in Figure 16. There was good agreement between Keio and KI ( $r = 0.84$ ) with an average for all specimens of  $0.51 \mu\text{g/l.}$  at Keio and  $0.45 \mu\text{g/l.}$  at KI. The scatter of the SWRI results is greater, but the average of all eight specimens,  $0.60 \mu\text{g/l.}$  is close to the average of the other laboratories.

The epidemiological studies were carried out with these methods, but an additional comparison of analysis at SWRI and KI was carried out (method study IV, Table 1). In this study SWRI distributed 10 urine frozen specimens with normal low concentrations. The results for the 10 specimens were in a close range and therefore only the averages are compared. At SWRI the average was  $0.23 \mu\text{g Cd/l}$  (S.D. = 0.065) and at KI the average was  $0.39 \mu\text{g Cd/l}$  (S.D. = 0.076).

Considering all the methods studies together, it seems as if analysis at Keio and KI gives similar results, and that these results, at least for elevated concentrations, agree well with NA analysis. The results from SWRI are more uncertain but may on a group basis agree relatively well with the results from the other laboratories.

All the urinary concentrations in the epidemiological studies of the Japanese and the Swedish group were corrected for specific gravity to the average specific gravity in the Swedish group (1.020). Specific gravity was not measured in the American group, but the average for a similar group studied earlier (29) was 1.021. No corrections for specific gravity were done for the American data. The average for the Japanese group in the cooperative study was also 1.021.

## Cadmium in Urine

In Japan a sample of 609 persons in the age range 0-90 years were studied (49). These were people coming to test their urines in a health center in Tokyo because high cadmium concentrations in soil were found in the area where they lived. However, it was found that consumption of local food was rare, and there were no indications that the daily cadmium intake in their area was higher than in other parts of Tokyo (58). All specimens were analyzed by Keio with the method given above. This study was carried out before the cooperative studies were started in the other countries. No data on smoking habits were collected.

In the U.S., 87 men from Dallas in the age range 1-70 were studied (25). They were volunteers among hospital staff and service club members. None of them had occupational exposure to cadmium. The urines were analyzed by SWRI with the method given above. In Sweden a sample of 130 persons (59) were selected for the study in the following way. From a roster of nonsmoking-concordant monozygotic male twin pairs living in Stockholm persons were contacted until five complete volunteer pairs in each 10-year age group from 10-69 years were found. In the same way 10 complete female nonsmoking pairs in the age group

Table 9. Cadmium concentrations in urine.

|       |     | Cd concentration, $\mu\text{g/l}$ .                  |                              |      |                                 |   |                              |      |                                 |  |                              |       |                                 |
|-------|-----|--|------------------------------|------|---------------------------------|---|------------------------------|------|---------------------------------|--|------------------------------|-------|---------------------------------|
|       |     | Japan (Tokyo)<br>Smokers and nonsmokers <sup>a</sup> |                              |      |                                 | U.S.A. (Dallas)<br>Smokers and nonsmokers |                              |      |                                 | Sweden (Stockholm)<br>Nonsmokers only <sup>a</sup> |                              |       |                                 |
| Age   | Sex | <i>n</i>   | Mean $\pm$ S.D. <sup>b</sup> |      | Mean $\times$ S.D. <sup>c</sup> | <i>n</i>                                  | Mean $\pm$ S.D. <sup>b</sup> |      | Mean $\times$ S.D. <sup>c</sup> | <i>n</i>   | Mean $\pm$ S.D. <sup>b</sup> |       | Mean $\times$ S.D. <sup>c</sup> |
| 0-9   | M   | 18   | 0.42                         | 0.28 | 0.35 1.83                       | 15  | 0.42                         | 0.31 | 0.33 1.86                       | 6  | 0.17                         | 0.018 | 0.17 1.1                        |
|       | F   | 15   | 0.58                         | 0.55 | 0.42 2.23                       | —   | —                            | —    | —                               | 2  | 0.23                         | —     | 0.22 —                          |
| 10-19 | M   | 29   | 1.00                         | 0.78 | 0.79 1.99                       | 8   | 0.33                         | 0.18 | 0.28 1.67                       | 10   | 0.20                         | 0.10  | 0.18 1.6                        |
|       | F   | 28   | 1.01                         | 1.16 | 0.66 2.50                       | —   | —                            | —    | —                               | —  | —                            | —     | —                               |
| 20-29 | M   | 23   | 1.40                         | 2.01 | 0.80 2.88                       | 16  | 0.42                         | 0.25 | 0.32 2.15                       | 10   | 0.23                         | 0.09  | 0.21 1.5                        |
|       | F   | 21   | 1.24                         | 1.18 | 0.90 2.23                       | —   | —                            | —    | —                               | —  | —                            | —     | —                               |
| 30-39 | M   | 45   | 1.44                         | 1.05 | 1.20 1.90                       | 7   | 0.50                         | 0.34 | 0.45 1.84                       | 10   | 0.31                         | 0.16  | 0.28 1.7                        |
|       | F   | 41   | 1.77                         | 1.32 | 1.42 1.94                       | —   | —                            | —    | —                               | —  | —                            | —     | —                               |
| 40-49 | M   | 52   | 1.71                         | 1.16 | 1.42 1.85                       | 16  | 0.80                         | 0.43 | 0.75 1.54                       | 10   | 0.31                         | 0.09  | 0.29 1.3                        |
|       | F   | 73   | 1.85                         | 1.25 | 1.53 1.85                       | —   | —                            | —    | —                               | 10   | 0.55                         | 0.44  | 0.46 1.7                        |
| 50-59 | M   | 48   | 1.62                         | 0.70 | 1.49 1.51                       | (50+)                                     | 0.70                         | 0.48 | 0.64 1.70                       | 10   | 0.51                         | 0.29  | 0.45 1.7                        |
|       | F   | 52   | 2.04                         | 1.22 | 1.75 1.74                       | 24  | —                            | —    | —                               | 10   | 0.71                         | 0.29  | 0.66 1.5                        |
| 60-69 | M   | 41   | 1.90                         | 0.99 | 1.68 1.63                       |   |                              |      |                                 | 10   | 0.40                         | 0.12  | 0.38 1.4                        |
|       | F   | 53   | 1.60                         | 0.94 | 1.38 1.72                       |   |                              |      |                                 | —  | —                            | —     | —                               |
| 70-79 | M   | 30   | 1.94                         | 1.19 | 1.65 1.76                       |   |                              |      |                                 | 11   | 0.63                         | 0.29  | 0.57 1.6                        |
|       | F   | 24   | 1.73                         | 1.07 | 1.47 1.77                       |   |                              |      |                                 | —  | —                            | —     | —                               |
| 80-89 | M   | 6  | 1.28                         | 0.63 | 1.15 1.59                       |   |                              |      |                                 | 9  | 0.43                         | 0.22  | 0.36 2.0                        |
|       | F   | 8  | 1.43                         | 0.56 | 1.33 1.46                       |   |                              |      |                                 | —  | —                            | —     | —                               |

<sup>a</sup> In Japan and Sweden the concentrations were adjusted to specific gravity = 1.020.

<sup>b</sup> Arithmetic mean and standard deviation.

<sup>c</sup> Geometric mean and standard deviation.

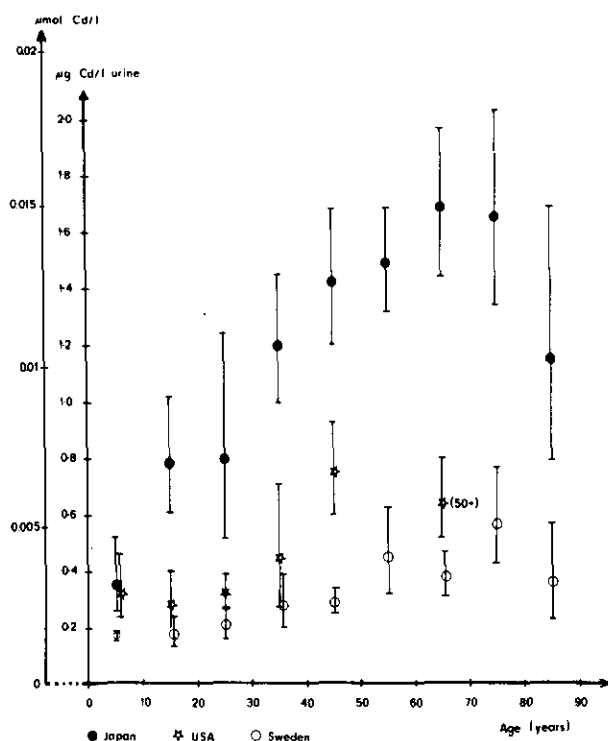


FIGURE 17. Average cadmium concentrations in urine of men in the three countries: (Japan, USA) smokers and nonsmokers; (Sweden) nonsmokers only; 95% confidence intervals of mean indicated.

40-59 and 10 complete male smoking-discordant pairs in the age group 40-59 were selected. Ten volunteers under age 10 and in each of the age groups 70-79 and 80-89 were also studied. All specimens were analyzed by KI with the method given above.

The distributions of individual urinary cadmium concentrations within any one age group fitted more closely to log-normal than to normal distributions. This was tested in the Swedish study (59) and is seen also in Figure 15 for the age group 30-59 years. In Table 9 the results are given for the three countries both as arithmetic and geometric means and standard deviations. There is a tendency for increasing urinary cadmium concentrations with age, which is more clearly shown in Figure 17 for men from the three countries. In the age groups 0-9 and 40-59 where both female and male data are available in Japan and Sweden there were systematically higher average concentrations for women than for men (Table 9). An earlier American study (29) of 216 men and women from Houston had not shown such a difference between the sexes.

Smoking habits do influence urinary cadmium excretion. In the age range 40-59, 10 smokers had on average 110% higher values than 10 nonsmokers (59) corresponding to about 0.3  $\mu\text{g/l}$ . difference. In the same age group there were nine American smokers in the study with an average urinary cad-

mium concentration of 1.0  $\mu\text{g/l.}$ , whereas the 31 nonsmokers had an average of 0.67  $\mu\text{g/l.}$  giving a difference of 0.33  $\mu\text{g/l.}$  An earlier American study (29) had given similar differences between smokers and nonsmokers.

In general the urinary cadmium levels agree with earlier reports from nonpolluted areas (9, 60-62). The levels of highly exposed persons and among certain rural groups in Japan have been higher (63-66).

The urinary cadmium concentrations in the Japanese group are, depending on the age group, two to five times higher than in the group of nonsmoking Swedes (Fig. 17). The difference can be explained only to a small degree by the inclusion of smokers in the Japanese group. The American group has results in between the Japanese and Swedish groups.

## Blood and Urine as Indicators of Exposure and Body Burden

Due to the long half-time of cadmium in the critical organ as well as in several other tissues, it would be of value for epidemiological studies and for individual occupational health monitoring to be able to measure exposure levels, total dose, body burden and the cadmium concentration in critical organs via some easily accessible indicator medium like urine, blood, hair, nails, or feces.

The best way to evaluate these relationships would be to carry out longitudinal studies of cadmium levels in various tissues of people with sudden changes in their cadmium exposure. Cross-sectional studies comparing exposure levels, body burdens, and cadmium concentrations in indicator media could also be of value for quantifying the relationships. One aim in the cooperative study was to analyze cadmium in blood and urine from newly employed cadmium workers at regular intervals during one year after employment. In each of the three countries as many as feasible, but not more than 25 workers, should be followed up during one year of exposure. Unfortunately the study could only be carried out in Sweden.

### Longitudinal Study of a High-Exposure Population

During one year there were 17 newly employed workers in a Swedish cadmium-nickel battery factory who could be followed during the whole first year of exposure. Morning urine specimens and blood specimens were collected at three times before employment, twice a week during the first two

weeks, twice a month during the next two months, and then once a month up to one year after start of employment. There were nine women and eight men, and the age range was 18-53 years. Samples of dust in factory air were collected for 8 hr with personal portable sampling devices on membrane filters on the same days as the blood and urine collections for three of the participants. Cadmium concentrations in blood and urine were measured by KI with the methods described above and in the dust samples with AA analysis after dissolution of the membrane filters in  $\text{HNO}_3$ .

The average cadmium concentration in blood before exposure started was 2.9 ng Cd/g for the three nonsmokers and 4.6 ng Cd/g for the 11 smokers. The corresponding concentrations in urine were 0.6 and 0.7  $\mu\text{g Cd/g creatinine.}$

An example of how the cadmium levels in blood and urine changed with time is given in Figure 18. The blood level increased progressively during the first 3 months and then leveled off. No obvious change in urine level took place during the first year of exposure. The pattern of change was similar in most of the other workers studied, but there was a considerable individual variation in the quantitative increase of average blood levels. The increase was greater among smokers than among nonsmokers. The short-term variations in cadmium concentrations in air did not seem to influence the cadmium concentrations in blood and urine. The sudden increase in average exposure caused the changes in the blood levels. The average cadmium concentration in air of this factory at the time of the study was about 50  $\mu\text{g Cd/m}^3$  air (67) and 95% of the dust particles had a MMAD less than 5  $\mu\text{m.}$  A one-compartment exponential model was fitted by a nonlinear regression procedure to the blood data. The median half-time of cadmium in blood was 77 days (range 8-14300 days). The detailed data from this study will be published elsewhere (Kjellström et al., to be published).

It was concluded that cadmium concentrations in blood would be an indicator of the average recent cadmium exposure over a time period of 1-3 months, whereas urine would not be a good indicator of recent exposure; at least not under the exposure conditions of this study. The half-time of cadmium in blood may be a reflection of accumulation in the lungs or in the blood cells.

### Cross-Sectional Studies of the General Population on Exposure via Food and Tobacco Smoking

By comparing the data in the previous sections, an evaluation can be made of how exposure, body

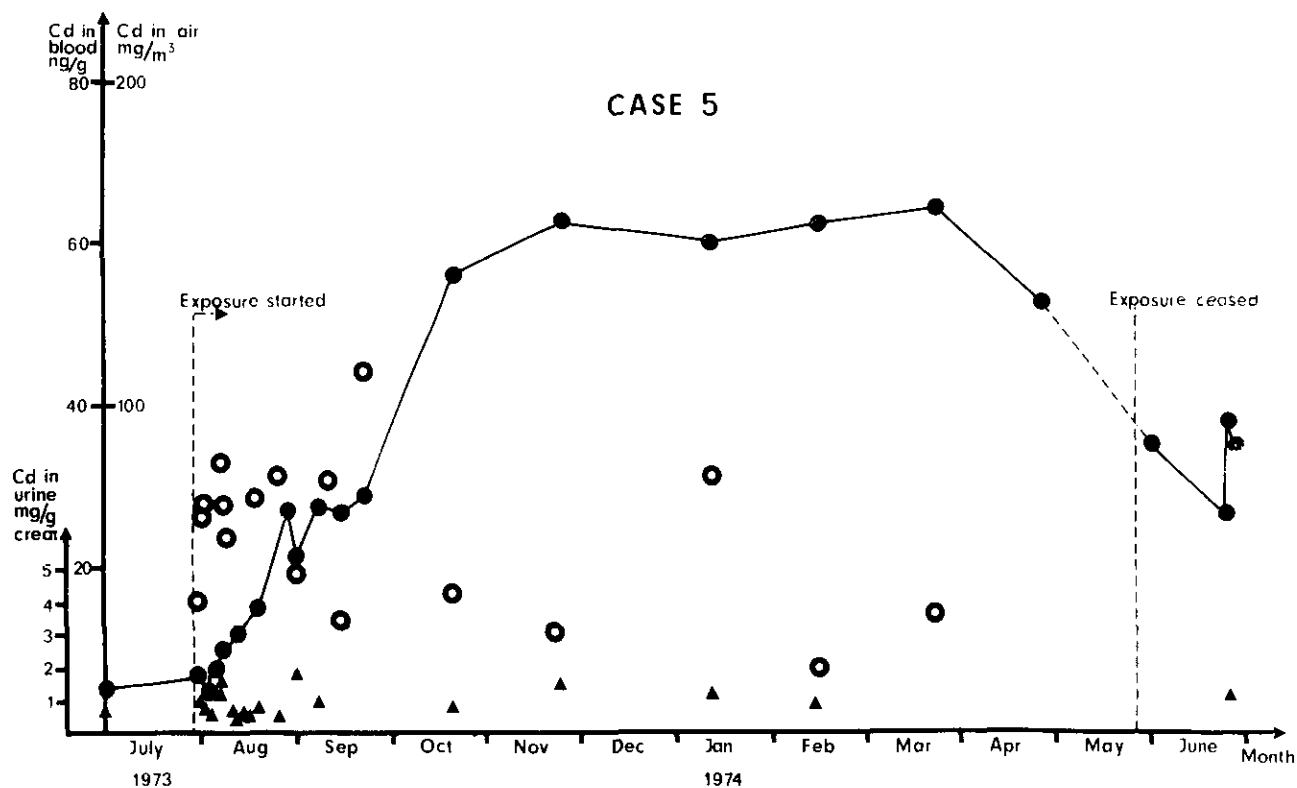


FIGURE 18. Cadmium concentrations in (○) air, (●) blood, and (▲) urine of a worker during the first year of occupational cadmium exposure.

Table 10. Average tissue and whole body weights (wet weights) in different age groups.<sup>a</sup>

| Age | Race      | Whole body kg | Energy intake MJ | Kidneys, g | Liver, g | Pancreas, g | Muscles, g <sup>b</sup> | Blood, g <sup>c</sup> | Other tissues (remainder), g | Urine, volume, l./24 hr |
|-----|-----------|---------------|------------------|------------|----------|-------------|-------------------------|-----------------------|------------------------------|-------------------------|
| 5   | Caucasian | 18.9          | 7.6              | 103        | 575      | 22          | 7560                    | 1512                  | 9128                         | 0.60                    |
|     | Japanese  | 17.8          | 7.6              | 97         | 542      | 21          | 7120                    | 1424                  | 8597                         | 0.60                    |
| 15  | Caucasian | 53.1          | 11.3             | 220        | 1280     | 60          | 21240                   | 3770                  | 26530                        | 0.98                    |
|     | Japanese  | 53.0          | 11.3             | 220        | 1278     | 60          | 21200                   | 3763                  | 26480                        | 0.98                    |
| 25  | Caucasian | 73.9          | 12.6             | 300        | 1500     | 70          | 29560                   | 5085                  | 37385                        | 1.0                     |
|     | Japanese  | 58.8          | 11.6             | 240        | 1194     | 56          | 23520                   | 4046                  | 29746                        | 1.0                     |
| 35  | Caucasian | 75.3          | 12.0             | 295        | 1500     | 70          | 30120                   | 5196                  | 38119                        | 1.0                     |
|     | Japanese  | 58.8          | 10.9             | 230        | 1171     | 55          | 23520                   | 4057                  | 29766                        | 1.0                     |
| 45  | Caucasian | 75.8          | 11.4             | 290        | 1500     | 70          | 30320                   | 5230                  | 38390                        | 1.03                    |
|     | Japanese  | 58.0          | 10.1             | 222        | 1148     | 54          | 23200                   | 4002                  | 29775                        | 1.03                    |
| 55  | Caucasian | 74.8          | 10.8             | 285        | 1500     | 70          | 29920                   | 5161                  | 37864                        | 0.96                    |
|     | Japanese  | 56.2          | 9.4              | 214        | 1127     | 53          | 22480                   | 3878                  | 28449                        | 0.96                    |
| 65  | Caucasian | 73.5          | 10.1             | 280        | 1500     | 70          | 29400                   | 5072                  | 37178                        | 0.93                    |
|     | Japanese  | 54.2          | 8.6              | 206        | 1106     | 52          | 21680                   | 3740                  | 27416                        | 0.93                    |
| 75  | Caucasian | 71.2          | 9.4              | 275        | 1500     | 70          | 28480                   | 4913                  | 35962                        | 0.85                    |
|     | Japanese  | 50.8          | 7.9              | 196        | 1070     | 50          | 20320                   | 3505                  | 25658                        | 0.85                    |

<sup>a</sup> Compiled from Documenta Geigy, 1970 (68). It is assumed that the ratio between Caucasian and Japanese tissue weights are the same as between the whole body weights at each age. Energy intakes are estimated from the Recommended Dietary Allowances (69).

<sup>b</sup> Muscles = 40% of body weight (55).

<sup>c</sup> 80 (age 5), 71 (age 15) and 69 (age 25–75) ml/kg body weight.

Table 11. Data used to calculate body burden of men in Japan (smokers and nonsmokers), USA (nonsmokers), and Sweden (nonsmokers).<sup>a</sup>

| Age | Country | Kidneys,<br>$\mu\text{g/g}^b$ | Liver,<br>$\mu\text{g/g}$ | Pancreas,<br>$\mu\text{g/g}$ | Muscle,<br>$\text{ng/g}$ | Body burden,<br>$\text{mg}^c$ | Urine,<br>$\mu\text{g}/24 \text{ hr}$ | Feces,<br>$\mu\text{g}/24 \text{ hr}^d$ |
|-----|---------|-------------------------------|---------------------------|------------------------------|--------------------------|-------------------------------|---------------------------------------|---|
| 5   | Japan   | 0.52                          | 0.23                      | 0.19                         | 60                       | 0.94                          | 0.22                                  | 25.0                                    |
|     | USA     | (1.9)                         | (0.43)                    | (0.13)                       | (15)                     | 0.65                          | 0.20                                  | 14.3                                    |
|     | Sweden  | 2.0                           | 0.33                      | 0.09                         | (5.5)                    | 0.48                          | 0.09                                  | 14.0                                    |
| 15  | Japan   | 14.1                          | 1.9                       | 0.77                         | 80                       | 8.6                           | 0.77                                  | —                                       |
|     | USA     | 3.5                           | 0.60                      | 0.24                         | 20                       | 2.3                           | 0.27                                  | 17.4                                    |
|     | Sweden  | 4.7                           | 0.55                      | 0.17                         | (7.3)                    | 2.0                           | 0.21                                  | 17.7                                    |
| 25  | Japan   | 20.0                          | 3.3                       | 1.18                         | 120                      | 13.9                          | 0.80                                  | 36.0                                    |
|     | USA     | 5.6                           | 0.94                      | 0.29                         | 36                       | 5.1                           | 0.34                                  | 12.8                                    |
|     | Sweden  | 5.0                           | 0.52                      | 0.28                         | 11                       | 2.9                           | 0.28                                  | 18.0                                    |
| 35  | Japan   | 34.8                          | 2.2                       | 1.08                         | 130                      | 16.1                          | 1.20                                  | —                                       |
|     | USA     | 7.6                           | 0.89                      | 0.36                         | 38                       | 5.7                           | 0.43                                  | 19.3                                    |
|     | Sweden  | —                             | —                         | —                            | 24                       | —                             | 0.37                                  | 16.8                                    |
| 45  | Japan   | 28.9                          | 4.5                       | 1.41                         | 210                      | 20.4                          | 1.42                                  | —                                       |
|     | USA     | 9.0                           | 1.2                       | 0.61                         | 70                       | 8.3                           | 0.73                                  | 17.0                                    |
|     | Sweden  | —                             | —                         | —                            | 38                       | —                             | 0.32                                  | 12.2                                    |
| 55  | Japan   | 43.6                          | 2.8                       | 1.59                         | 220                      | 21.5                          | 1.43                                  | 45                                      |
|     | USA     | 8.9                           | 1.1                       | 0.45                         | 64                       | 7.7                           | 0.56                                  | 18.3                                    |
|     | Sweden  | 6.5                           | 0.48                      | 0.27                         | 62                       | 6.0                           | 0.40                                  | 12.0                                    |
| 65  | Japan   | 22.0                          | 2.7                       | 1.21                         | 340                      | 20.9                          | 1.56                                  | —                                       |
|     | USA     | —                             | —                         | —                            | —                        | —                             | —                                     | —                                       |
|     | Sweden  | 9.0                           | 0.72                      | 0.40                         | 94                       | 8.6                           | 0.39                                  | 9.5                                     |
| 75  | Japan   | 30.0                          | 3.7                       | 1.16                         | 300                      | 20.9                          | 1.40                                  | —                                       |
|     | USA     | —                             | —                         | —                            | —                        | —                             | —                                     | —                                       |
|     | Sweden  | 5.0                           | 0.94                      | 0.40                         | —                        | —                             | 0.41                                  | —                                       |

<sup>a</sup> Assumed cadmium concentration in blood = 3 ng/g in all three countries.

<sup>b</sup> Kidney concentrations assumed to be  $\frac{2}{3}$  of kidney cortex concentrations.

<sup>c</sup> Concentration in other tissues assumed to be 0.64 times concentration in muscle. All the concentrations are geometric averages.

<sup>d</sup> Feces amounts are arithmetic averages.

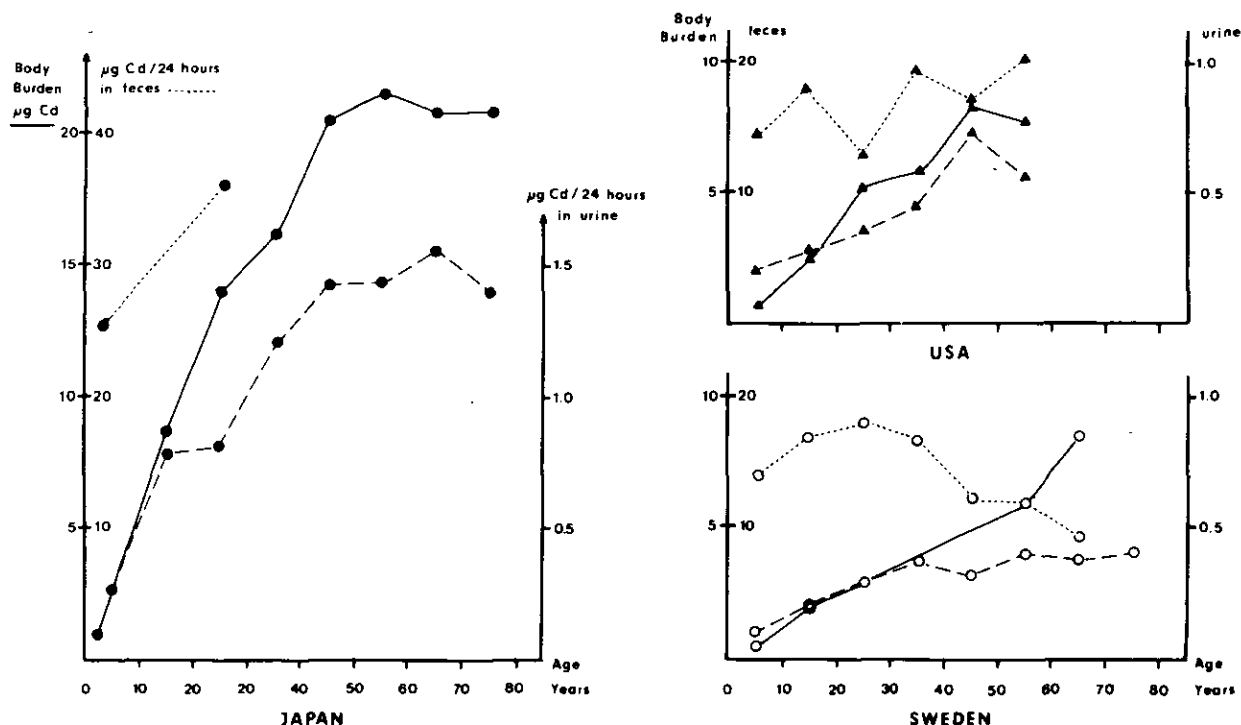


FIGURE 19. Comparison of daily fecal cadmium amounts, daily urinary cadmium excretions, and calculated body burdens: (USA, Sweden) nonsmokers only; (Japan) smokers and nonsmokers.



burden, and excretion interrelate.

For calculations of body burden or urinary excretion, age-specific data on average tissue weights and daily urine volume are needed. Because the American data on cadmium levels in the various tissues were limited to males, it was decided to make the calculations based on male data in all three countries. From general biological handbooks the data in Table 10 were collated. For some tissues intrapolations had to be made. It was assumed that muscle weight was 40% of body weight (55) at all ages, even though this value refers to adults. Weights for the individual tissues among Japanese were not available and it was assumed that the weight distribution between tissues was the same as for caucasians. Urine volumes were assumed to be the same in all three countries—1 liter/24 hr among young adults, with lower volumes in childhood and old age. The volumes given in Table 10 were estimated from data in Documenta Geigy 1970 (68), as well as data reviewed by Elinder et al. (59).

The cadmium concentrations (geometric averages for nonsmoking men) used for the calculation of body burdens and daily intake are given in Table 11. For the younger age groups in the U.S. and Sweden, estimates of certain tissue concentrations were based on the assumption that all subjects were nonsmokers and the increase with age would follow the same pattern as in Japan. The cadmium concentrations in blood was assumed to be 3 ng/g in all countries and all ages.

The daily intake via food in the U.S. and Sweden could be estimated roughly as the cadmium amount in feces because the fecal data were based on data for groups of nonsmokers. For Japan no individual information on smoking habits were collected, but the data were included for comparison.

It is seen in Figure 19 that there is a good agreement between daily cadmium amount in urine and body burden and bad agreement between these two variables and estimated cadmium daily intake via food. The pattern is the same in all three countries, even though in the Japanese data smokers were included. About 0.005–0.01% of body burden is excreted daily in urine.

For the 30–59 year age group, a comparison between nonsmoking and smoking men was carried out in order to quantify the role of smoking habits as a determining factor for cadmium body burden and excretion. In the U.S., sufficient data for both smoking categories on cadmium in kidney cortex, liver, muscle, and urine were available. It is seen in Figure 20 that for each tissue the geometric mean concentration is about twice as high for smokers as for nonsmokers. In Sweden some data on smokers and nonsmokers was also available (47). Using the

weights given in Table 10 the body burdens for smokers and nonsmokers (age 30–59) in the U.S. and Sweden were calculated. Urinary excretions, daily intake, and cadmium concentrations in blood were also estimated from the data given earlier in this report. A comparison between the different variables (Table 12) shows how the smokers have higher levels than the nonsmokers. In an average smoker of age 45 in the U.S. and Sweden, tobacco smoking in itself accounts for about half the body burden and half the urinary excretion.

In Sweden there were not enough data on muscle from smokers and nonsmokers, so an estimate was made based on overall muscle data (Table 12). The calculated body burdens were higher for smokers than for nonsmokers. Only nine muscle samples from nonsmokers were analyzed, however.

In the U.S. there were sufficient data to calculate the additional body burden due to smoking in each age group (Table 13). The calculation was based on the differences in average tissue cadmium concentrations between smokers and nonsmokers. The accumulation with age would correspond to a constant intake from smoking up to the highest age group where the slight decrease may reflect a shorter overall smoking duration (cohort effect). There were not enough data on urine and feces to estimate smoking-specific values.

The additional body burden due to smoking at age 45 would be about 4–6 mg (Tables 12 and 13). The body burden of cadmium for a nonsmoking Swede or American at age 45 would be about 5–6 mg. In Japan at this age about 75% of the male population smoke on average 24 cigarettes per day (70). If we assume that the smoking-related 4–6 mg of the American body burden is the result of smoking 20 cigarettes per day, the part of the average Japanese body burden (21 mg, Table 8) that is explained by smoking would be about 3.6–5.4 mg. Thus the calculated body burden for nonsmoking Japanese would be about 16–17 mg Cd. About 80% of the Swedish and American autopsy cases were smokers

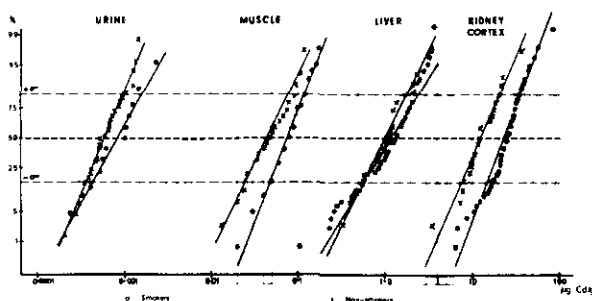


FIGURE 20. Cumulative distribution of cadmium concentrations in four tissues of male smokers and nonsmokers at age 30–59 in the U.S.

**Table 12. Comparison of cadmium concentrations in tissues and calculated body burdens of smokers and nonsmokers in U.S. and Sweden at age 30-59.**

| Tissue                         | USA        |         | Sweden            |                   |
|--------------------------------|------------|---------|-------------------|-------------------|
|                                | Nonsmokers | Smokers | Nonsmokers        | Smokers           |
| Kidney cortex, $\mu\text{g/g}$ | 12.4       | 24.0    | 11.8              | 21.9              |
| Liver, $\mu\text{g/g}$         | 1.0        | 1.2     | 0.57              | 0.86              |
| Pancreas, $\mu\text{g/g}$      | 0.44       | 0.66    | 0.36              | 0.61              |
| Muscles, $\text{ng/g}$         | 47         | 70      | (29) <sup>a</sup> | (48) <sup>a</sup> |
| Blood, $\text{ng/g}$           | 3          | 4       | 3                 | 4                 |
| Calculated body burden, mg     | 6.5        | 12.7    | 4.9               | 8.2               |
| Urine                          |            |         |                   |                   |
| $\mu\text{g/24 hr}$            | 0.60       | 0.80    | 0.36              | 0.72              |
| % of body burden               | 0.009      | 0.006   | 0.007             | 0.009             |
| Feces, $\mu\text{g/24 hr}^b$   | 16.7       | 19.5    | 15.9              | 19.1              |

<sup>a</sup> These figures were estimated from the whole group studied (including those for whom smoking habits were unknown). The average for this group was 40 ng/g. The ratio between smokers and nonsmokers was set the same as for pancreas. In the American data the muscle ratio and pancreas ratio between smokers and nonsmokers were similar.

<sup>b</sup> The age group 20-59 was used in order to increase the study populations and to get a more reliable estimate of average fecal cadmium amount.

**Table 13. Difference between smokers and nonsmokers in average cadmium concentration in tissues and average body burden in the U.S.**

| Age | Cd concentration         |                        |                           |                        | Additional body burden, mg <sup>a</sup> |
|-----|--------------------------|------------------------|---------------------------|------------------------|---|
|     | Kidneys, $\mu\text{g/g}$ | Liver, $\mu\text{g/g}$ | Pancreas, $\mu\text{g/g}$ | Muscles, $\text{ng/g}$ |   |
| 15  | 1.7                      | 0.20                   | 0.10                      | 0                      | 0.64                                    |
| 25  | 3.4                      | 0                      | 0.13                      | 0                      | 1.0                                     |
| 35  | 7.4                      | 0.40                   | 0.18                      | 3                      | 3.0                                     |
| 45  | 7.8                      | 0.01                   | 0.10                      | 36                     | 4.3                                     |
| 55  | 7.6                      | 0                      | 0.31                      | 35                     | 4.0                                     |

<sup>a</sup> Calculated in the same way as the body burdens in Table 11. The additional cadmium concentration in blood from smoking is assumed to be 1 ng/g.

(Table 8). This can explain the differences between body burden estimates in Table 8 and Table 12.

## General Discussion and Conclusions

The study showed that there was a good agreement between the different laboratories in the final step of the analysis and therefore any differences between analytical results of the individual materials would be caused by losses or interferences in the preparatory chemical steps of analysis, or matrix effects in final analysis.

The method studies showed that in tissues with high levels (about 1  $\mu\text{g/g}$ ) of cadmium, like the liver, the agreement between analysis at different laboratories was good. Analysis of muscles with average levels about 0.1  $\mu\text{g/g}$  did not give such good agreement, and further development work on methods is necessary. Accurate muscle analysis data are of great importance to further quantify the half-time in muscles, which seems to be much longer than in liver and kidney. In food stuffs with low cadmium concentrations (0.01-0.1  $\mu\text{g/g}$ ) large differences in analytical results occurred. Data that

are not accompanied by valid method studies must be evaluated cautiously. One useful approach is to compare completely different analytical techniques. Such a comparison showed that it is possible to get a good agreement between atomic absorption and neutron activation analysis at levels above 0.01  $\mu\text{g/g}$ . In tissues with low concentrations (about 1 ng/g) such as urine and blood, the matrix effects on analysis were still a problem because urine analysis gives comparable results in different laboratories whereas blood analysis still may give considerable differences. However, when data on blood cadmium concentrations from different groups of people are produced within one lab using the same method, relative differences between such groups may still be used for evaluations.

The studies on daily intake of cadmium by analysis of cadmium amount in feces showed that within each country the cadmium concentration in feces tends to be relatively constant regardless of age. The daily amount of feces varied with age in a similar fashion as energy intake and were similar in the three countries. The daily amount of cadmium in feces from Japan was about twice as high as in the U.S. and Sweden. Due to the low gastrointestinal

absorption these data would be representative for the differences in daily cadmium intake via food.

There were indications that the daily cadmium intake in Sweden may have increased during the 20th century but no comparable data were available from Japan and the U.S. The data from Sweden were not conclusive, however, and further studies of old food and tissue specimens would be of value.

The cadmium concentrations in kidney cortex, liver, pancreas, and muscle as well as the calculated body burden showed similar differences as the daily intake, but there was a tendency for a higher ratio between data from Japan and the other data than was found for daily intake. The rapid accumulation with age of cadmium in liver and kidney cortex seen in earlier studies was confirmed. There was a continuous accumulation in muscles even at old age, which indicates that the half-time in muscle is longer than in kidney cortex. Further autopsy studies of cadmium in muscles are necessary and in such studies other major tissues like fat, bone and skin should be analyzed with sensitive methods that can determine changes at the 0.001–0.01  $\mu\text{g Cd/g}$  level. The tissue specimens from the autopsies carried out in this cooperative study are stored frozen in tissue banks. They can be used for analyses in the future.

Women in many age groups had higher tissue cadmium concentrations than men. In the Swedish group there was the same proportion of smokers among men and women. Differences in smoking habits between the sexes can not explain the differences in tissue concentrations. Whether the higher values for women are the result of higher cadmium intakes per unit body weight, higher absorption rates, or lower excretion rates is not known.

There seemed to be a greater proportion of body burden in liver among the Japanese than among the Americans and Swedes, possibly reflecting a different distribution of cadmium in the body at high exposure levels. From the American and Swedish data it was estimated that smokers would get an additional body burden at age 45 of about 4 mg through absorption of cadmium from tobacco smoke. With a rough assumption that the contribution to body burden from smoking would be the same in all countries, it was calculated that the body burdens of a nonsmoking adult male would be 16–17 mg in Japan, and 5–6 mg in the U.S. and Sweden. The daily cadmium intakes via food were about 35  $\mu\text{g}$  in Japan and 17  $\mu\text{g}$  in the other countries.

The cadmium concentration in urine among adults after correction for individual variations in specific gravity had a log-normal distribution. Urinary cadmium excretions increased with age. In older age groups from Japan there was a slight de-

crease in urinary excretion of cadmium which did not occur in Sweden. On a group basis after long-term low level exposure urinary excretion of cadmium was a good indicator of body burden. After sudden changes in exposure level, cadmium concentration in blood was a better indicator of recent intake than cadmium concentration in urine. The comparisons between daily intakes of cadmium via food and body burdens as well as the data on urinary excretion did not indicate any change in whole body half-time of cadmium depending on exposure level.

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